SURGERY

VOL. 10 JULY, 1941 NO. 1

Original Communications

Society of University Surgeons, St. Louis, Mo., Feb. 14 and 15, 1941

THE ROLE OF EPITHELIZATION AND CONTRACTURE IN THE HEALING OF THE PEPTIC ULCER

A PRELIMINARY REPORT

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THE question of just how chronic the peptic ulcer really is and what is the nature of its chronicity needs further consideration. It is not known, for example, whether the chronic state results from the destruction of a large amount of stomach wall with terminally slow healing or whether only a small amount of tissue is originally destroyed and an inhibiting factor or factors keep the defect open. In this preliminary report an attempt is made to evaluate the chronicity of healing of artificial gastric defects resulting from the destruction of known amounts of the various tissue layers of the stomach wall and to compare the healing of these defects both grossly and microscopically with pathology of the peptic ulcer.

METHOD

Known amounts of mucosa alone, muscle and serosa, and all three layers were excised from the anterior wall of the prepyloric area of the stomachs of fully anesthetized dogs. When all three layers were removed, the omentum was sutured over the remaining defect. The dogs were returned to their regular diets and killed at various intervals. The size of the resulting lesion was measured and microscopic sections cut.

RESULTS

Up to 4 square inches of mucosa were removed and the defects healed without showing any signs of chronicity. Contraction of the stomach

Presented at the meeting of the Society of University Surgeons, at St. Louis, Mo., Feb. 14 and 15, 1941.

wall occurring immediately after cutting and during healing accounted for most of the closure. A reduction in size amounting to as much as 25 per cent of the original was observed to take place as soon as the stomach was allowed to resume its natural position again in the abdominal cavity. During healing, these defects of the mucosa alone did

Fig. 1.—Healing of mucosal defect. The muscle is intact and over it is a layer of young fibrous tissue without surface necrosis. A thin layer of epithelium is extending from normal mucosa on either side.

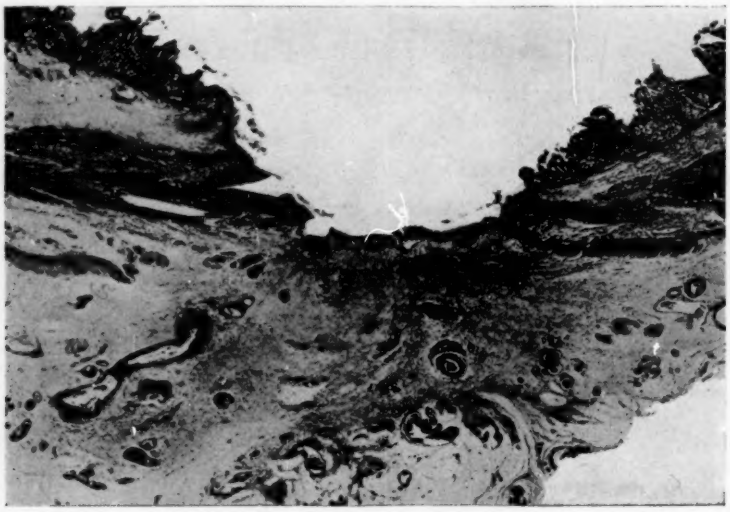

Fig. 2.—The usual anatomy of the chronic peptic ulcer. The muscles are separated by a fibrous base with surface necrosis. This fibrosis extends beyond the wall of the stomach where there are many thrombosed vessels. The epithelium is not regenerating. (After Hurst and Stewart.)

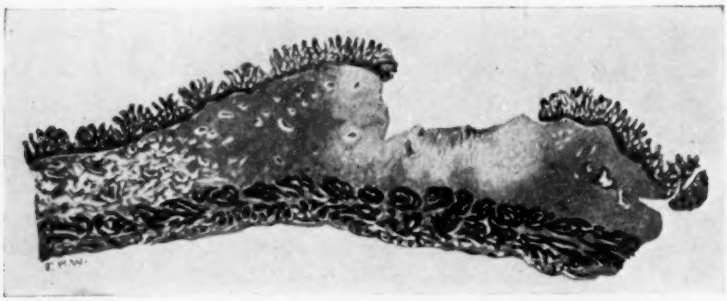

Fig. 3.—Atypical anatomy of chronicity. Muscle intact. Marked fibrosis under mucosa on either side. (After Hurst and Stewart.)

not resemble chronic peptic ulcer whatsoever. Epithelization began after the usual latent period. The cells at the edge of the defect arranged themselves in a single layer and extended across a narrow granulating base existing above intact muscle. (Fig. 1.) In distinct contrast, Hurst and Stewart[1] stress that 96 per cent of all chronic ulcers have destruction and replacement fibrosis of the muscle extending down to or beyond the serosa (Fig. 2). The other 4 per cent have either questionable chronicity or some degree of it because excessive fibrosis takes place between the muscularis mucosa and the muscle at the edge of the defect (Fig. 3).

Removal of 4 square inches of serosa and muscle without removal of mucosa did not result in any corresponding or smaller area of necrosis of the mucosa. Mucosal ulcerations did not take place during healing, although the underlying muscle was destroyed. The omentum spontaneously attached itself to the area where the muscle and serosa were removed, contraction reduced the size of this type of defect also, and as it grew smaller the omentum again began to separate.

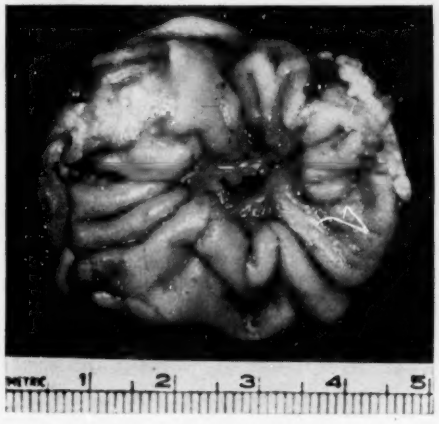

Fig. 4.—Gross appearance of the 1 inch square defect of all three layers after thirty days of healing.

When 1 square inch of all three layers of the stomach wall was destroyed, a defect resulted which after thirty days of healing was of the size of the chronic peptic ulcer or slightly larger and exactly resembled its microscopic picture (Figs. 4, 5, and 6). The muscle was separated and its base was all fibrous tissue with surface necrosis. Epithelization had begun to occur, but irregularly at one or the other edge, and was small in amount. It is of interest that the granulating bed of one of these defects was oozing blood when the animal was killed on the twenty-seventh day. Larger areas of muscle up to 4 square inches in size have also been destroyed in conjunction with a 1 square inch defect of mucosa. Destruction of this additional amount of muscle did not seem to contribute to chronicity more than the destruction of equal amounts of all three layers. In either case the ulcer was of approximately the same size after the same interval. Contraction of muscle occurred after

the larger amount was destroyed for microscopically it could be seen at the edge of the defect.

DISCUSSION

How long defects of various sizes of all three layers of the stomach wall will remain open and what will be the effect on their healing with

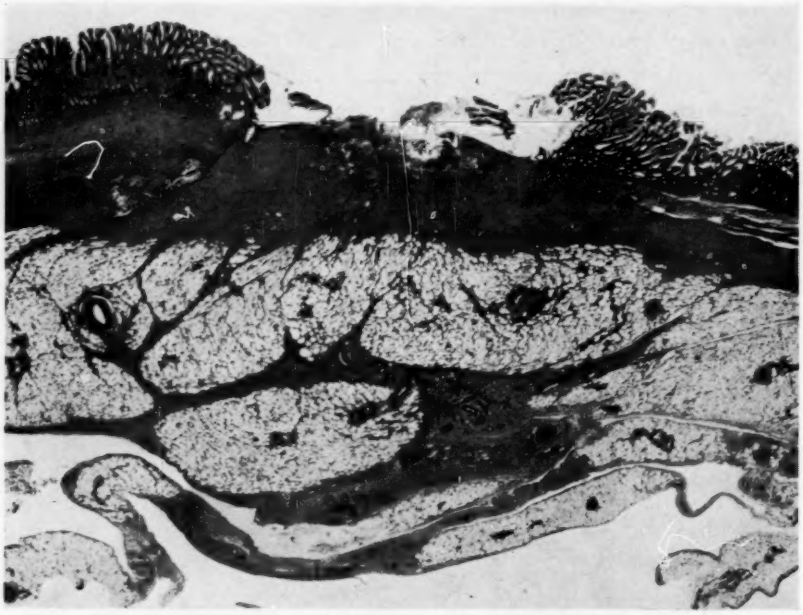

Fig. 5.—Microscopic appearance of a similar defect after twenty-seven days of healing. Muscle seen only on the left. Fibrous base with surface necrosis. Fibrosis extends beyond the stomach wall and contains many thrombosed vessels. The epithelium is not regenerating.

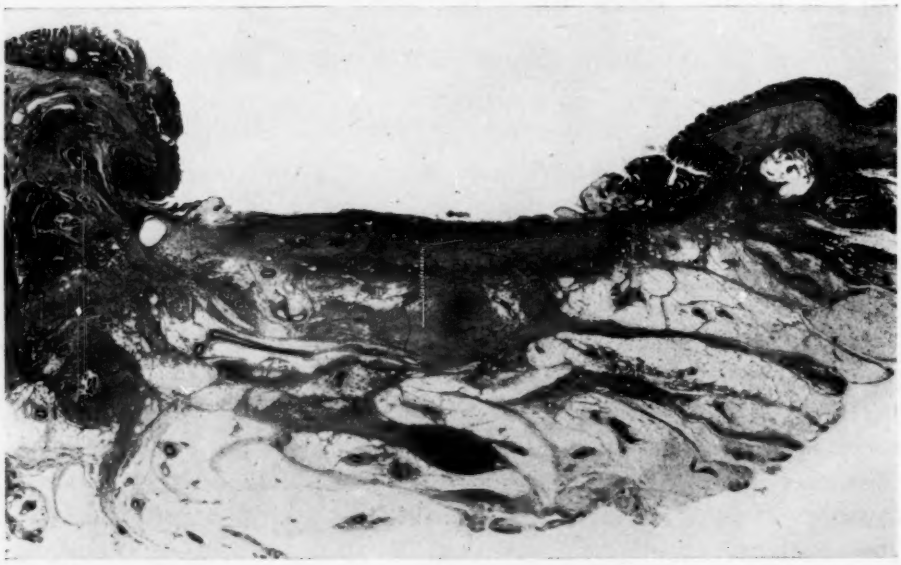

Fig. 6.—Microscopic appearance of another similar defect after thirty days of healing. Muscle seen only on the left. Epithelium regenerating somewhat on both sides. Surface necrosis not as marked.

an irregular secretion or an unusual quantity of acid and pepsin will be reported later. Certainly when mucosa and only part of the muscle were destroyed, Flood and one of us (E. L. H.)[2] could only temporarily delay healing although enough acid and pepsin were given over a sufficient length of time to digest the experimental animal. Only a few of these lesions perforated and the rest healed in two or three weeks. At the end of one week, however, most of them exhibited the characteristics of the chronic peptic ulcer; namely, overhanging or nonproliferating epithelial edges and fibrosis or granulations with surface necrosis replacing the muscle. To the contrary, these three layer defects with an omental patch still showed all the signs of chronicity at the end of a month, although there had been no alteration in their chemical environment during healing.

It is important to realize that the resemblance of chronicity can be duplicated in so short a period of time as a week or ten days. Duplication, then, is only significant when it continues to exist. The number of agents and methods which will produce this duplication with or without associated gastritis and multiple ulcerations are legion: surgical duodenal drainage, cinchophen poisoning, parenteral aspirin, brain tumors in the region of the basal ganglia, continuous stimulation of the vagus, avitaminosis, irregular and prolonged gastric secretion from ingestion of alcohol, caustics, irritants, and chronic histamine stimulation, upper respiratory infections, and many others. With many of these methods the animals die either from perforation or from other debilitating or toxic effects associated with the method of production soon after the ulcer is produced. Chronicity is simulated, but the animals never live long enough to find out whether the lesions are actually chronic. Usually, when the debilitating or toxic action is removed, the lesions promptly heal. Only recently with cinchophen[3] and chronic histamine stimulation[4] has there been some hope of carrying out real chronic experiments. The method herein described offers an experimental opportunity to separate and evaluate destructive action and the factors producing chronicity. Both may be related, of course.

This work further suggests that the chronicity of peptic ulcer may in many instances be caused by the destruction of larger amounts of tissue than is usually supposed or that contraction is eliminated in some way. Because perforations are pin point, because mucosal ulcerations are of small diameter when acute, and because the actual size of the chronic ulcer rarely exceeds 1.5 cm., it is generally assumed that the amount of tissue destroyed is necessarily small and some inhibiting factor keeps it open. To the contrary, evidence is presented that relatively larger amounts of tissue may be originally destroyed, and contracture brings the area down to a size consistent with the usual chronic peptic ulcer.

Clinically, the ulceration of the stomach either heals, perforates, or becomes chronic. Despite the presence of acid everywhere, the chronic

ulcer occurs largely on the lesser curvature where destruction extends into the mesentery or in the posterior wall where it extends into the pancreas or into an adherent lesser sac (76 per cent of chronic ulcers occur in these two locations), or on the anterior wall into a lapel of the liver, or into some surrounding adherent organ. The anatomical coincidence of the involvement of three layers of the stomach wall and the fixation of this point in some manner with negation of the forces of contraction forms a pattern of healing which cannot be neglected as a factor determining the chronicity of the peptic ulcer of the stomach.

SUMMARY

1. Contraction plays a large role in the closure of any defect in the wall of the stomach.

2. Destruction of all three layers of the wall of the stomach repaired with a patch of omentum produces during healing the gross and microscopic picture of the chronic peptic ulcer.

3. The microscopic pathology of chronic peptic ulcer can be duplicated in ten days, but this similarity is only significant when it continues to exist over a subsequent period of time.

4. After healing for thirty days, a 1 square inch defect of all three layers of the stomach wall still had the appearance of chronicity, although there had been no change in its chemical environment during healing.

5. Because of contraction, the size of the chronic peptic ulcer may misrepresent the amount of tissue which was originally destroyed; or if not, then contraction must be inactivated in some way during healing.

6. Most experimental methods of producing peptic ulcer have simply duplicated the pathologic picture of chronicity and have not yet indicated whether the lesion will continue to have this appearance over some period of time.

7. The method herein described offers an opportunity to test whether the destructive factors which produce the pathologic picture of peptic ulcer will also cause chronicity.

8. The anatomy of the chronic peptic ulcer contributes to its chronicity.

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AUTOGENOUS CARTILAGE GRAFTS

An Experimental Study

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OUR knowledge concerning cartilage transplantation is in a somewhat confused state at present. This is due to reports of clinically successful transplantations not only of autogenous grafts, but also of homogenous grafts, and even of so-called "refrigerated isografts." This confusion is undoubtedly abetted by the fact that cartilage is an avascular tissue which probably lives largely by lymph diffusion, and because it requires so little for sustenance, degenerative changes take place quite slowly. Hence clinical observations may be of questionable value as the period of observation may be too short to determine the ultimate fate of the transplant.

CLINICAL EVIDENCE

Autogenous.—Clinically there is a well-founded belief that autogenous rib cartilage grafts live when transplanted to almost any location and that they neither increase nor decrease in size. It is also believed that they change little microscopically, other than undergoing that calcification which normally occurs. There are many reports in the literature concerning their successful clinical use.

Living Homogenous.—Living homogenous grafts have not been extensively used clinically, but because of the great difficulties encountered in satisfactorily restoring the ear, Gillies[1] in 1937 attempted and reported the successful transplantation of maternal auricular cartilage to the son, in the correction of traumatic and congenital microtia. Following this report, others have reported on this procedure as being practicable. J. B. Brown[2] in 1940 reported clinically successful cases of rib cartilage transplants from father and mother to sons, in the correction of traumatic deformities of the nose and orbit.

Dead Cartilage.—Dead preserved transplants of both animal and human cartilage were used rather extensively two decades and more ago. These were employed mainly in the correction of saddle noses. The procedure was gradually discarded because it was believed that these inserts were absorbed.

Within the past ten years there has been a revival of the use of these so-called preserved homografts. These are not in the strict sense of the word grafts, for I do not believe that even their staunchest advocates

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would consider them to be living tissue. They are dead cartilage removed from cadavers and preserved in one way or another.

In 1938 O'Connor and Pierce[3] reported on what they call "refrigerated cartilage isografts." Rib cartilage from a cadaver is preserved under sterile precautions in a solution of one part 1:1,000 aqueous merthiolate to four parts of normal saline solution in the refrigerator. They report the use of cartilage stored for as long as two years. Of 375 transplants done, 6 became infected, of these only 1 was totally lost. They state that after five years the transplants still maintained their original size and identity.

In 1940 Kirkham[4] reported the successful use of cadaver auricular cartilage, preserved in the same manner, in reconstruction of subtotal losses of the ear.

From these clinical reports one would conclude that either living autogenous or homogenous cartilage can be successfully transplanted, and that dead homogenous cartilage will persist as a foreign body in the tissues for a long period of time without loss of size.

EXPERIMENTAL EVIDENCE

Autogenous.—The experimental data available would indicate that the clinical belief concerning autogenous cartilage grafts is correct. In 1917 Davis[5] found that cartilage grafts remain of original size when transplanted subcutaneously in dogs with one end of the graft in contact with bone, while similar experiments with bone grafts show that they are gradually completely absorbed.

Loeb[6] in 1926 reported that of the cartilage grafts from various sources autografts are tolerated with less reaction and with less eventual loss of substance.

In 1938, Peer[7] showed that in man autogenous cartilage grafts retained their normal structure and were not absorbed or invaded. This conclusion was based on microscopic examination of segments of costal cartilage buried beneath the chest skin and removed at intervals of six months to six years.

In 1940, Kirkham[4] showed microscopic sections of autogenous rib cartilage which had been stored in the abdominal subcutaneous tissues of a patient for ten years and had not lost its cartilaginous characteristics.

Homogenous Grafts.—Experimental data concerning homogenous living transplants of cartilage are quite scarce. Loeb and Siebert[8] report that there is greater tissue reaction to, and more eventual absorption of, homogenous cartilage grafts than of autogenous.

Dead Homogenous Implants.—The experimental work concerning dead homogenous implants is also rather meager. Peer[7] reported that

he had buried cadaver rib cartilage preserved in alcohol under the skin of patients and then removed the implants at intervals of seven days up to two years. Histologic examination of the removed specimens showed that a rather intense inflammatory reaction takes place at once. A thick connective tissue capsule forms about the implant, walling it off. This reaction lasts about a month and then largely disappears. The cartilage then acts as an inert but tolerated foreign body up until about nine months. From then on there is progressive invasion of the cartilage by fibrous tissue and partial absorption takes place.

Kirkham's[4] findings using the ear cartilage from rabbits differs somewhat from this. He was attempting to find out how long after death a homogenous transplant would be possible. A rabbit was killed and five pieces of auricular cartilage removed one hour after death. Two of these were placed on ice dry, and two moistened in Ringer's solution on ice. The fifth piece was implanted in the abdominal wall of another rabbit. Each hour up to six hours after death another piece of cartilage was removed and put in the abdomen of a living rabbit. At twenty-four hours and forty-eight hours the iced cartilage was implanted. Six months later the implants were removed and sectioned. They were all intact with the exception of the dry, iced cartilage. On section they all showed the cell spaces vacuolated and the nuclei absent. His conclusions were that the cartilage retained its form even though cellular death occurred.

It seems to me that the entire subject should be reviewed experimentally. A start has been made in this direction, the results of which are herewith reported.

METHOD OF EXPERIMENT 1

Since there seems to be ample clinical and experimental evidence that autogenous rib cartilage grafts live and maintain their size over prolonged periods of time, it might seem unnecessary to add further data. However, to establish a base line for the series of experiments planned it seemed essential that quantitative data should be obtained.

In dogs, central ossification of the costal cartilages occurs quite early. For this reason young adult dogs were used in order to secure rib cartilage with as little central bone as possible. If moderate calcification was found near the bony rib-cartilage junction, this end of the costal cartilage was trimmed off until only cartilage was left.

Ten dogs were used in this experiment, the operations being carried out aseptically under ether anesthesia. Each dog was operated upon in the same manner.

An oblique incision was made over the right and left costal margins, the rib cage exposed, and three costal cartilages removed on each side. The perichondrium was stripped off of three of these. The remaining

TABLE I

AUTOGENOUS CARTILAGE TRANSPLANTS WITH PERICHONDRIUM

TIME GRAFT IN PLACE	ORIGINAL LENGTH AND WIDTH IN CM.	REMOVAL LENGTH AND WIDTH IN CM.	ORIGINAL WEIGHT IN GM.	REMOVAL WEIGHT IN GM.	CHANGE IN WEIGHT
2 wk.	6.7 × 0.6	8.0 × 0.4	0.808	0.508	−0.30
	6.2 × 0.7	6.1 × 0.6	1.143	0.857	−0.286
	5.6 × 0.3	5.7 × 0.2	0.192	0.180	−0.012
	7.4 × 0.5	7.6 × 0.4	0.918	0.960	+0.052
	6.8 × 0.6	6.5 × 0.5	0.810	0.783	−0.027
	5.2 × 0.45	5.0 × 0.4	0.282	0.216	−0.066
3 mo.	6.1 × 0.3	5.2 × 0.3	0.324	0.339	+0.005
	5.6 × 0.6	5.8 × 0.6	0.322	0.308	−0.014
	8.0 × 0.4	7.7 × 0.6	0.753	0.744	−0.009
	5.7 × 0.2	5.6 × 0.2	0.188	0.196	+0.008
	7.0 × 0.7	7.2 × 0.6	1.026	1.008	−0.008
	6.5 × 0.5	6.4 × 0.45	0.775	0.756	−0.019
6 mo.	5.0 × 0.5	4.8 × 0.5	0.181	0.207	+0.026
	6.0 × 0.3	5.8 × 0.3	0.315	0.336	+0.021
	6.2 × 0.6	6.2 × 0.5	0.988	0.978	−0.010
	5.5 × 0.6	5.7 × 0.6	0.308	0.329	+0.021
	6.7 × 0.6	6.9 × 0.5	0.810	0.867	+0.057
	7.0 × 0.4	7.0 × 0.5	0.623	0.638	+0.015
1 yr.	6.2 × 0.45	6.4 × 0.5	0.605	0.800	+0.195
	4.45× 0.6	4.7 × 0.45	0.240	0.300	+0.060
	5.2 × 0.4	5.0 × 0.5	0.198	0.221	+0.023
	4.4 × 0.3	4.5 × 0.3	0.112	0.108	−0.004
	7.0 × 0.5	7.0 × 0.5	0.776	0.728	−0.048
	6.5 × 0.4	6.4 × 0.4	0.561	0.532	−0.029
1½ yr.	5.6 × 0.6	4.5 × 0.5	0.311	0.222	−0.089
	5.5 × 0.5	5.6 × 0.5	0.704	0.669	−0.035
	7.6 × 0.7	7.0 × 0.7	0.610	0.531	−0.079
	5.5 × 0.5	5.0 × 0.5	0.305	0.261	−0.044
	6.0 × 0.5	5.8 × 0.4	0.588	0.517	−0.071
	5.0 × 0.5	4.7 × 0.5	0.196	0.181	−0.015

three were cleared of soft tissues as completely as possible, but the perichondrium was not disturbed. A small piece of each rib cartilage was saved for microscopic examination. Each segment of cartilage was measured, the length and breadth at the widest point recorded, and the weight determined on a chemical balance. The three cartilages with perichondrium were implanted in the subcutaneous tissues of the abdomen on the right side. One was placed in the epigastrium, one opposite the umbilicus, and one in the lower abdomen. The three without perichondrium were placed in parallel positions in the left anterior abdominal wall. Each piece of cartilage was inserted through a separate small incision one-half to one inch long. These wounds and the ones over the costal margins were closed with silk.

In all, sixty transplants were made, thirty with and thirty without perichondrium. The grafts were removed from two dogs at intervals of two weeks, three months, six months, one year, and one and one-half years. Thus six grafts with perichondrium and six grafts without perichondrium were made available for study at each time interval.

TABLE II

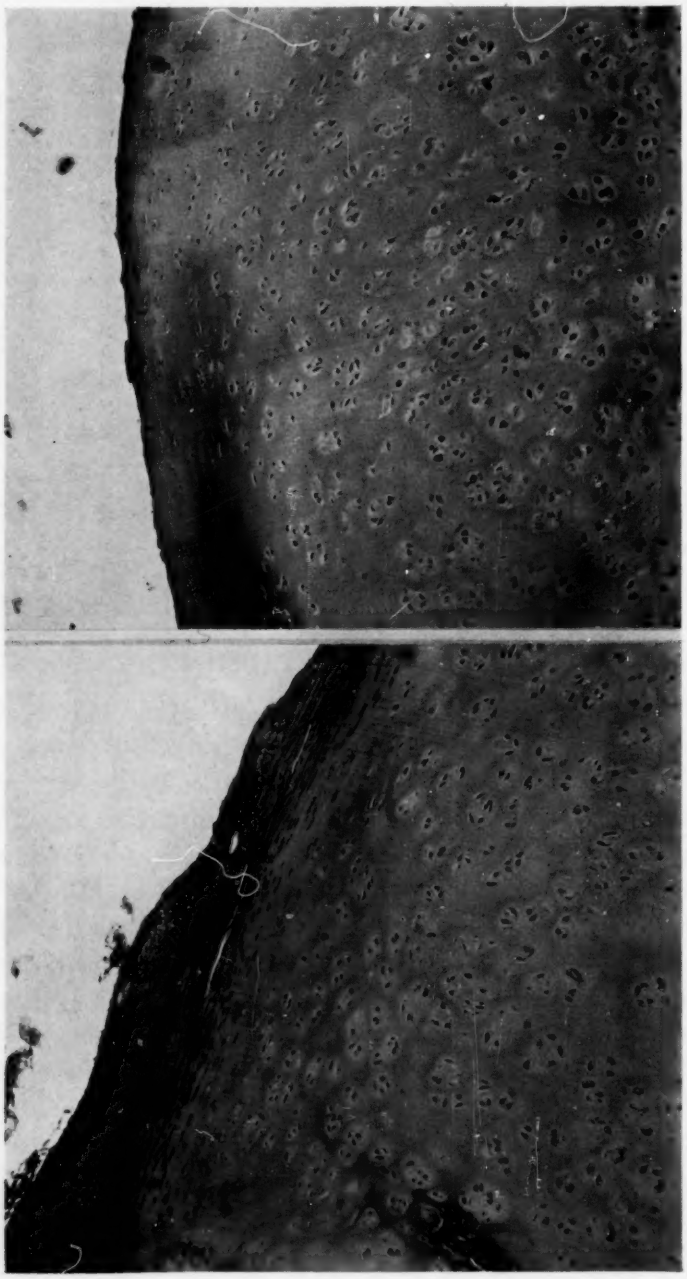
AUTOGENOUS CARTILAGE TRANSPLANTS WITHOUT PERICHONDRIUM

TIME GRAFT IN PLACE	ORIGINAL LENGTH AND WIDTH IN CM.	REMOVAL LENGTH AND WIDTH IN CM.	ORIGINAL WEIGHT IN GM.	REMOVAL WEIGHT IN GM.	CHANGE IN WEIGHT
2 wk.	7.7 × 0.5	8.1 × 0.5	0.909	0.740	−0.169
	6.5 × 0.6	5.9 × 0.35	0.329	0.188	−0.141
	6.0 × 0.5	6.0 × 0.5	0.308	0.295	−0.013
	5.5 × 0.4	5.7 × 0.4	0.288	0.178	−0.110
	4.2 × 0.3	4.5 × 0.3	0.115	0.128	+0.013
	7.8 × 0.5	8.2 × 0.5	0.875	0.712	−0.163
3 mo.	4.0 × 0.3	3.4 × 0.3	0.102	0.072	−0.030
	6.1 × 0.5	5.8 × 0.5	0.311	0.260	−0.051
	8.1 × 0.5	7.8 × 0.4	0.928	0.857	−0.071
	5.1 × 0.3	5.3 × 0.3	0.258	0.277	+0.019
	6.5 × 0.4	6.5 × 0.4	0.308	0.288	−0.020
	8.0 × 0.5	7.5 × 0.5	0.905	0.866	−0.039
6 mo.	5.0 × 0.25	5.0 × 0.3	0.204	0.217	+0.013
	7.5 × 0.5	7.8 × 0.5	0.878	0.905	+0.027
	4.8 × 0.3	5.0 × 0.3	0.197	0.205	+0.008
	7.0 × 0.6	7.4 × 0.6	0.585	0.631	+0.046
	4.6 × 0.4	5.2 × 0.5	0.312	0.388	+0.076
	8.0 × 0.5	7.5 × 0.4	1.021	0.975	−0.046
1 yr.	6.5 × 0.55	7.4 × 0.4	0.352	0.361	+0.009
	6.2 × 0.35	7.0 × 0.5	0.347	0.352	+0.005
	5.4 × 0.45	5.0 × 0.35	0.408	0.356	−0.052
	6.0 × 0.5	6.5 × 0.4	0.360	0.355	−0.005
	7.8 × 0.35	7.5 × 0.35	0.516	0.505	−0.011
	4.5 × 0.3	4.0 × 0.3	0.155	0.098	−0.057
1½ yr.	6.5 × 0.6	6.0 × 0.6	0.225	0.300	+0.075
	7.8 × 0.5	8.2 × 0.6	0.617	0.552	−0.065
	7.5 × 0.5	8.0 × 0.5	0.605	0.568	−0.037
	5.0 × 0.3	4.8 × 0.3	0.215	0.230	+0.015
	6.2 × 0.5	6.4 × 0.55	0.355	0.346	−0.009
	7.5 × 0.5	7.8 × 0.45	0.587	0.550	−0.037

GROSS EXAMINATION AND MEASUREMENT OF TRANSPLANTS

During the course of the experiment the transplants could be easily palpated under the skin and in most instances their outlines were visible. No graft was absorbed; all were recovered and studied. On removal it was found that they were rather loosely attached in the subcutaneous tissues. If on removal any soft tissue remained adherent, this was removed as carefully as possible. Inspection showed that the transplants still retained their cartilaginous characteristics. The grafts which had been longer in their new location in some instances showed small areas which had lost their translucent sheen. These spots were yellower than the surrounding hyaline-appearing cartilage and softer. In all instances the transplants were pliable and when bent still retained their springlike elasticity. The specimens were measured and it was found that their dimensions were practically the same as when originally transplanted. There were minor variations, but these were within the limits of error. The specimens were also weighed for comparison with the weights recorded at time of transplantation. It was found, here too,

that little change had occurred. In general both those grafts with and without perichondrium showed their greatest weight loss in the specimens removed two weeks after grafting. A minor weight loss was also noted in the three-month specimens. On the other hand, those grafts removed six months after transplantation showed on the whole a small gain in weight. There was then a small weight loss in general in those specimens which had been transplanted for a year and for one and one-half years. There was no significant difference in the quantitative be-



B.

A.

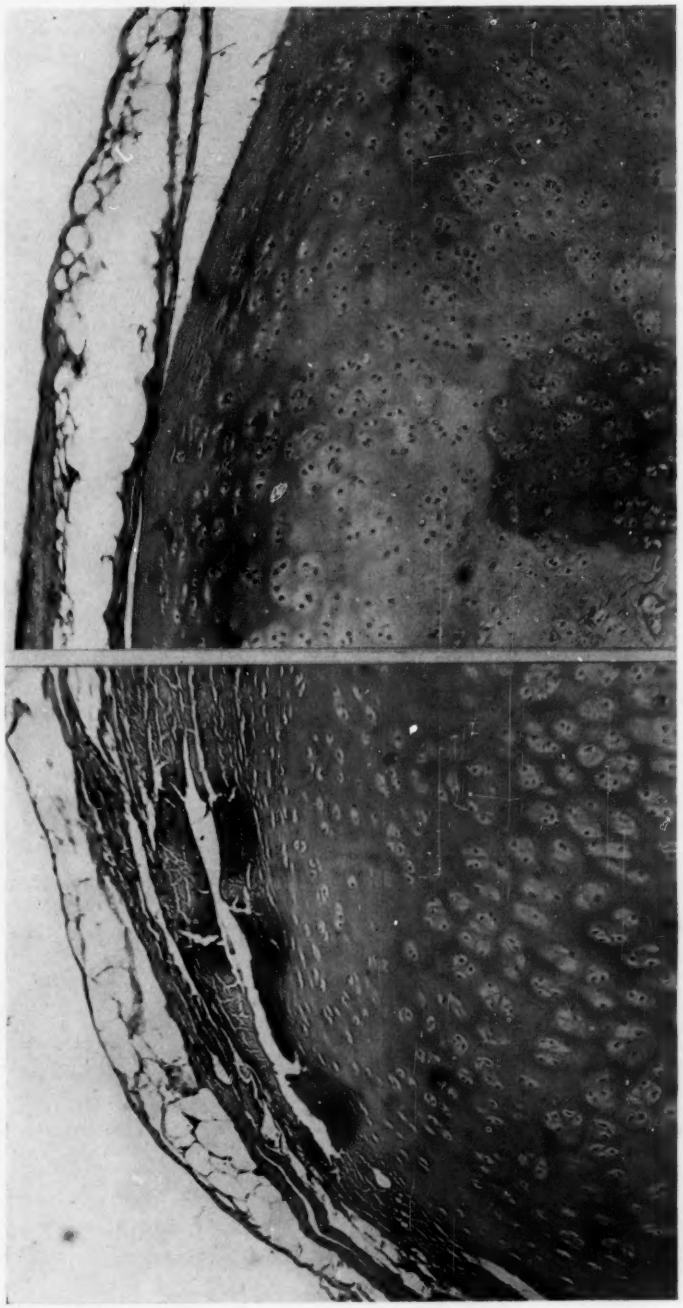
Fig. 1.—Photomicrograph (×100), showing the architecture normally seen in costal cartilage of young adult dogs. *A*, With perichondrium; *B*, without.

havior or the gross appearance in those grafts transplanted with, and those transplanted without, perichondrium.

The detailed data appear in Tables I and II.

MICROSCOPIC EXAMINATION

Sections were made for microscopic examination of all sixty grafts. The photomicrographs shown are representative ones selected from those studied at the various time intervals.



A. *B.*

Fig. 2.—Photomicrograph (×100). Costal cartilage after two weeks' transplantation to abdominal subcutaneous tissues. *A*, With perichondrium; *B*, without perichondrium.

One can state without question that these autogenous cartilage grafts remain living cartilage. In all specimens the cellular structure was found intact and cell nuclei present. As the grafts were in their new location for longer periods the cells in most instances appeared larger with a greater amount of clear area about the nuclei. In the older specimens central calcification was frequently observed, and in some in-

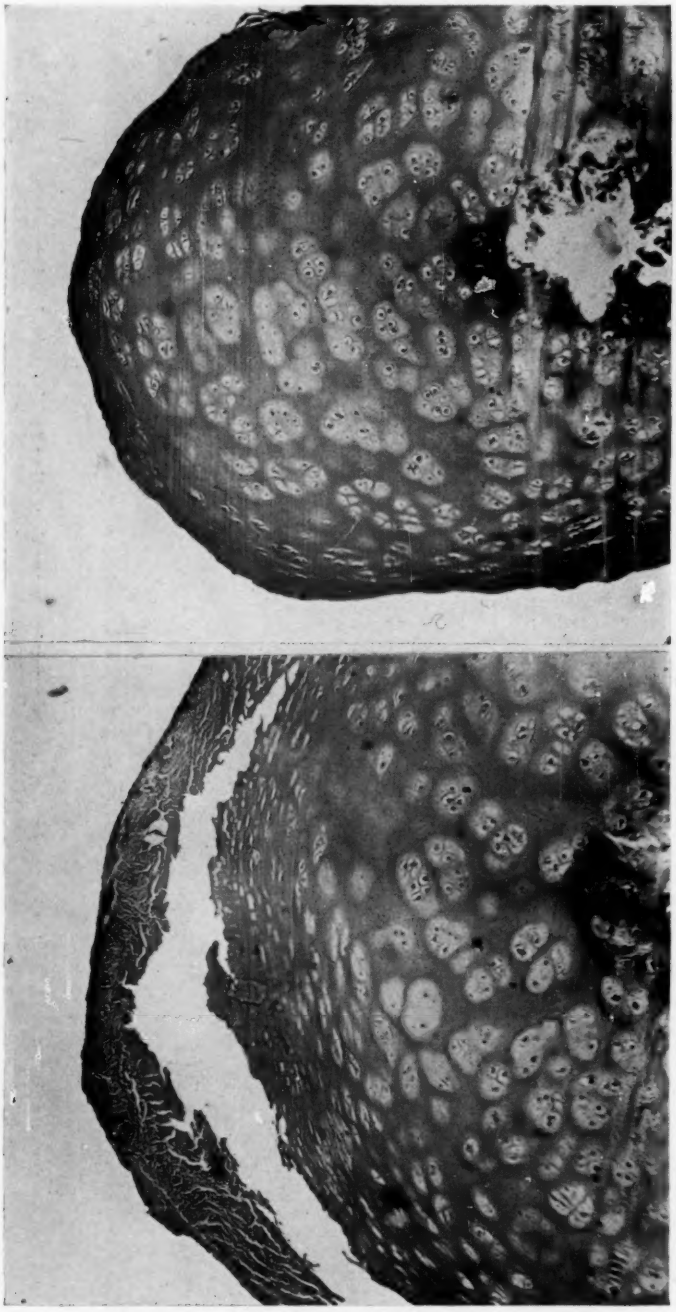
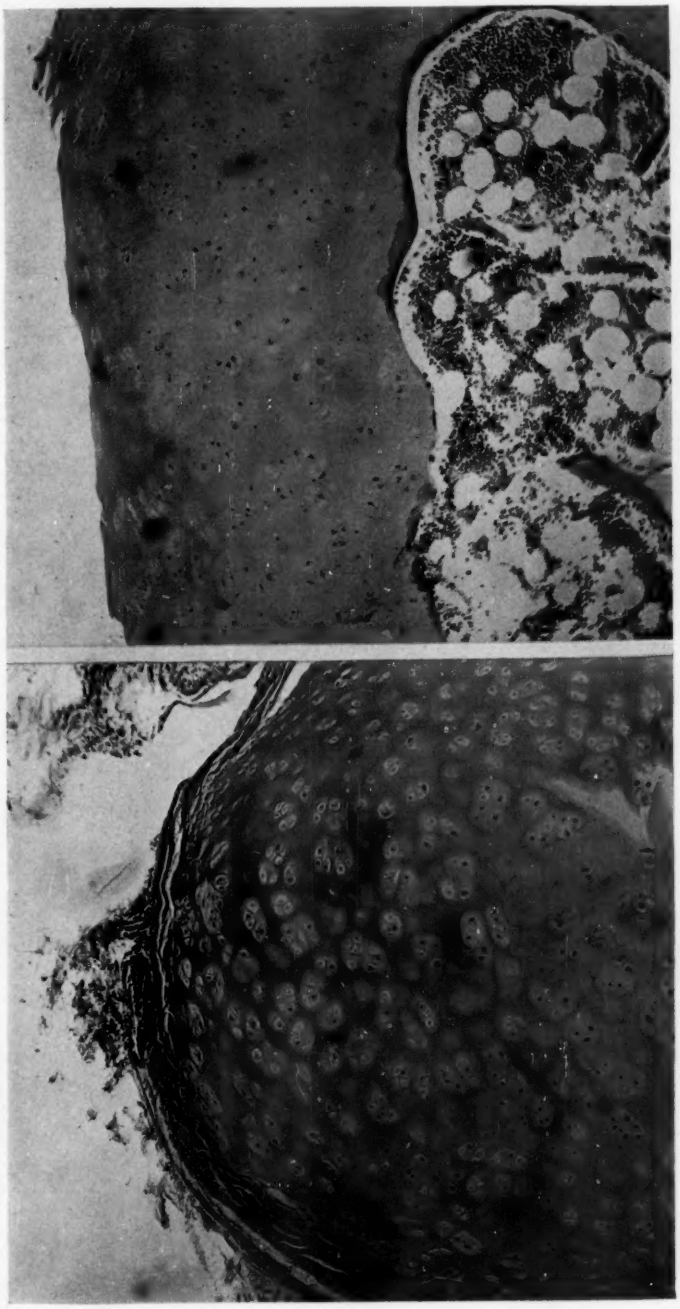


Fig. 3.—Photomicrograph (×100). Specimens of costal cartilage removed after three months in abdominal wall. *A*, With perichondrium shows moderate central calcification; *B*, transplanted without perichondrium also shows this. In both specimens there is some increase in the clear zones about the cell nuclei.

stances osteoid or actual bone formation occurred. In this centrally formed bone a marrow cavity was at times observed.

EXPERIMENT 2

While engaged in the foregoing experiment which is intended as a baseline experiment for similar studies to be carried out with living

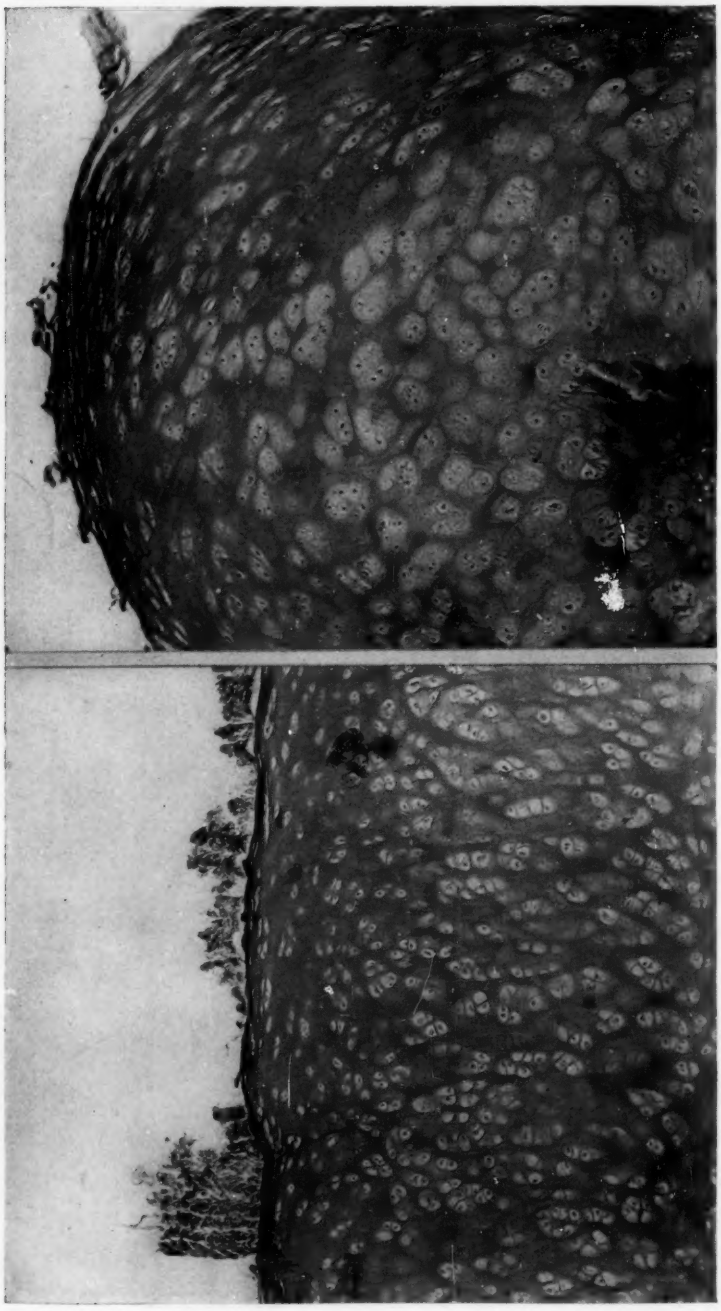


B.

A.

Fig. 4.—Photomicrograph (×100). Specimens removed from abdominal wall at six months. *A*, Transplanted with perichondrium, shows moderate increased size of the clear zones of the cells; *B*, transplanted without perichondrium, central bone marrow formation.

homogenous and zoögenous grafts and with dead autogenous, homogenous, and zoögenous implants, it occurred to me that it might be possible to grow thin sheets of cartilage by seeding small particles of living autogenous cartilage in a known location. Although this at first thought might seem to have little prospect of success, I had some encouragement from experiments previously completed[9] in which it had been observed



B.

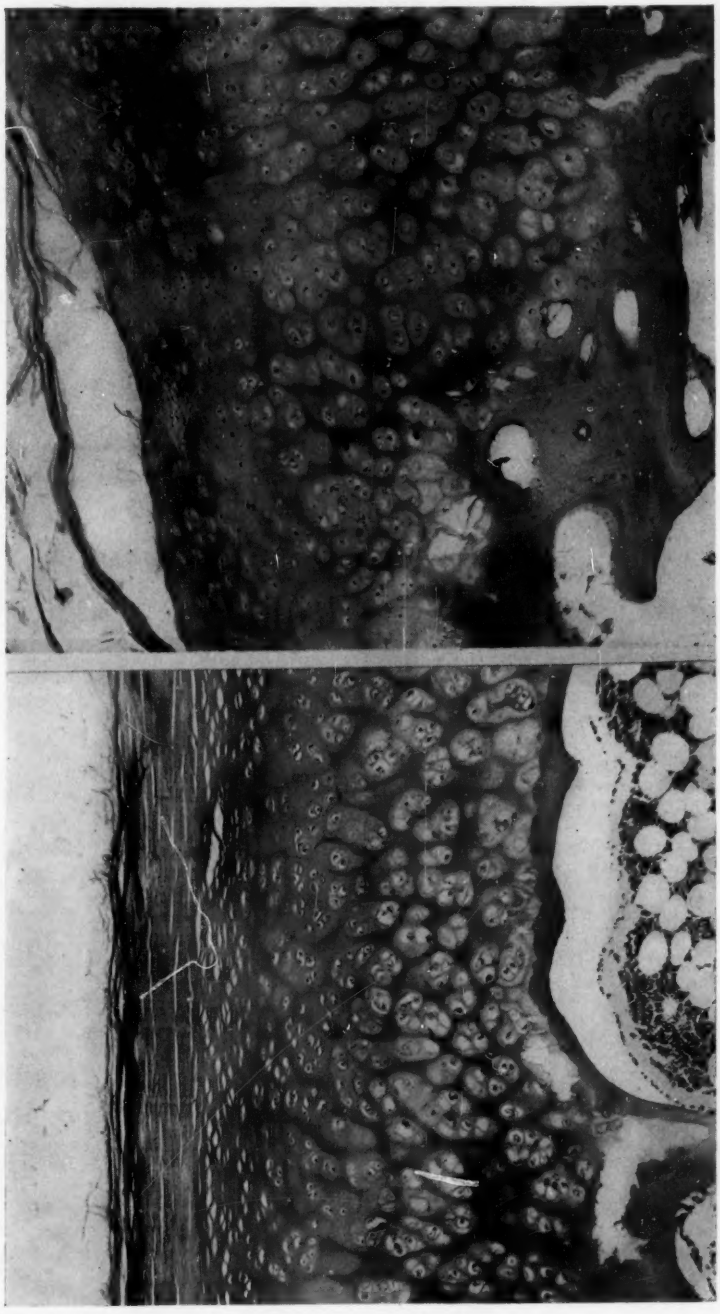
A.

Fig. 5.—Photomicrograph (×100). Specimens removed from abdominal wall at one year. Both *A* (with perichondrium) and *B* (without perichondrium) are well preserved.

that strips of rib cartilage placed side by side in the dog's knee joint seemed to heal together by cartilaginous fusion.

METHOD

Accordingly costal cartilages were removed as in the previous experiment. From one-half of these the perichondrium was removed. The cartilage was then chopped into fine particles. On the right side of the



B.

A.

Fig. 6.—Photomicrograph (×100). Specimens removed from abdominal wall one and one-half years after transplantation. Both *A* (with perichondrium) and *B* (without perichondrium) show moderate degenerative changes. There is central bone and marrow formation and some peripheral fibrous tissue invasion.

abdomen small incisions were made down to the rectus fascia, and the subcutaneous tissues separated from the fascia to make a small pocket. On the right side the chopped cartilage with perichondrium was placed in three depots, one on the upper, mid-, and lower abdomen. Chopped cartilage without perichondrium was placed in similar locations on the left side. This finely divided cartilage was spread out in a thin layer over the rectus fascia so that an area about one inch in diameter was covered and the subcutaneous tissues lay smoothly over it. The wounds were closed with silk. Four dogs in all were operated upon. The wounds were then opened at intervals of three months, six months, one year and one and one-half years.

GROSS APPEARANCE

Twenty-four specimens in all were examined, twelve with and twelve without perichondrium. In each instance a thin sheet of glistening, translucent, cartilaginous-appearing material about the size and shape of a half-dollar was recovered. Tiny rounded protuberances could be seen

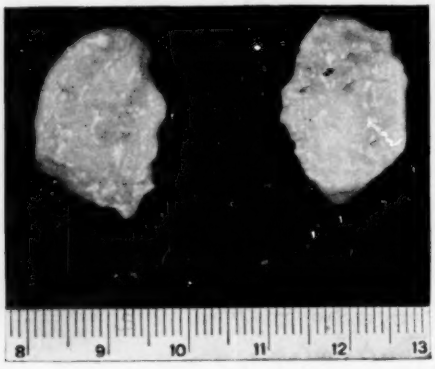


Fig. 7.—Gross appearance of masses removed at one and one-half years, following seeding of cartilage particles in a pocket over the rectus fascia.

on the homogenous surface of this mass which probably represented individual particles of cartilage. This thin sheet of opaque cartilaginous-appearing material had the springlike quality of cartilage. It could be bent to 50 to 60° without cracking and on release return to its original position and shape.

MICROSCOPIC EXAMINATION

These specimens were all sectioned and studied. It was found that there was no actual growth of cartilage of which one could be positive, but the particles of cartilage had become adherent to one another by fibrous tissue. The cartilage particles were all living as evidenced by the character of the cells. In the one-year and one-and-one-half-year specimens there was considerable bone and marrow formation noted in some of the cartilage particles.

CONCLUSIONS

From the two experiments reported it would appear that autogenous rib cartilage when transplanted to the subcutaneous tissues of the dog remains living and maintains its size and weight for as long as one and one-half years.

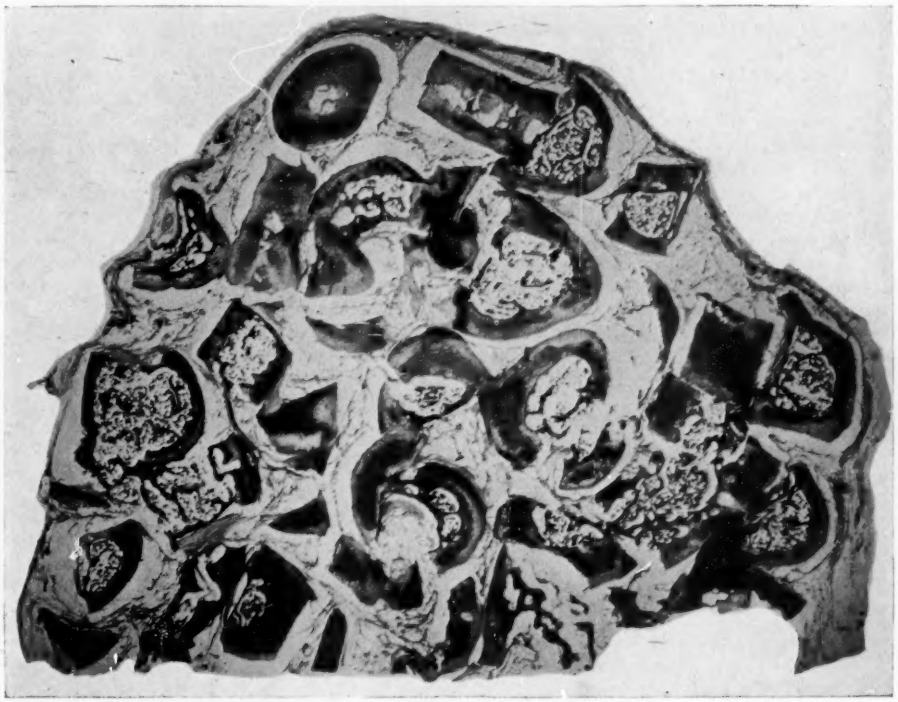


Fig. 8.—Photomicrograph (×8). Cross-section of specimen removed six months after seeding cartilage particles. The cartilage particles are connected by loose fibrous tissue.

Fig. 9.—Photomicrographs (×8). Specimen of cartilaginous mass produced by seeding which was removed at one and one-half years. There is bone formation in the center of most of the cartilage particles.

Autogenous rib cartilage, finely chopped and seeded over the rectus fascia in the dog, stays viable and fuses together into a solid sheet of opaque cartilage-like material. This fusion is by fibrous tissue. Grossly this mass has some of the properties of fibroelastic cartilage.

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STUDIES OF THE JUGULAR PRESSURE OF ANESTHETIZED DOGS DURING POSITIVE INFLATION OF THE LUNGS BEFORE AND AFTER PNEUMONECTOMY

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AS THE use of positive pressure anesthesia is being extended, the dangers that accompany its administration should be more generally appreciated. Recent discussions of the subject direct attention to the impairment of ventilation when positive pressure is continuous[1] and emphasize the importance of avoiding high pressures because of the danger of rupturing alveoli.[2,3] The effects of positive pressure ventilation on the circulation, however, seem to have been overlooked, or passed over in a few words. After emphasizing the mechanical effectiveness of his positive pressure apparatus, Crafoord,[1] for example, warns that "the only thing we have to follow closely is the circulation." He then dismisses the subject with just one additional sentence, in which he states that any failure of the circulation can be easily corrected by the intravenous administration of blood and stimulants.

In some of our previous studies it was shown that inflation of the lungs of anesthetized dogs caused a fall in cardiac output. In the first series of experiments this decrease in cardiac output was observed after thoracotomy and inflation of the lungs at pressures varying between 3 and 6 mm. of mercury.[4] In later experiments it was demonstrated that the decrease in cardiac output was proportional to the intratracheal pressure used.[5] Further studies have shown that a rise in both jugular vein and pulmonary artery pressures also occurs and that a similar rise in pulmonary artery pressure follows ligation of the pedicle of one lung.[6] Because in experiments done previous to all of these[7] it had been demonstrated by us that ligation of either primary branch of the pulmonary artery did not cause a change in cardiac output, it was suggested that the reduction in cardiac output accompanying positive pressure inflation was due to a tamponade effect caused by pressure of the inflated lungs on the mediastinum and heart rather than to pulmonary artery obstruction. Confirmation of this hypothesis is

Presented at the meeting of the Society of University Surgeons, at St. Louis, Mo., Feb. 14 and 15, 1941.

here presented by studies of the effect on venous pressure of inflation of the left lung after eliminating the possibility of tamponade by resecting the right.

METHOD

Direct measurements of the jugular pressure of five dogs, anesthetized with barbital sodium, were obtained with the apparatus of Moritz and von Tabora.[8] Because the base line cannot be very accurately adjusted to the level of the base of the heart, the absolute values of these measurements are of less interest than their relative changes, which are not affected by the base line, under the experimental conditions.

In every experiment a control reading was obtained with the anesthetized animal breathing normally. The trachea was then connected tightly with a metal cannula, through the inspiratory arm of which oxygen was introduced by means of a catheter passed loosely into the trachea as far as its bifurcation. A second control reading was obtained immediately after cannulation of the trachea with the animal breathing oxygen at atmospheric pressure. Arrangements were then made for controlling intratracheal pressure by means of a screw clamp on the expiratory arm of the cannula. Intratracheal pressure was measured by direct connection of the cannula with a water manometer. After the second control reading had been obtained, the intratracheal pressure was raised to about 3 cm. of water and the chest was opened wide by splitting the sternum and introducing a self-retaining retractor.

Then, with the chest wide open, a series of venous pressure readings was obtained while both lungs were inflated by increasing pressures. Each pressure was maintained for only two minutes. The right lung was then resected by clamping, dividing, and ligating the hilar structures of each lobe separately. A second series of venous pressure readings was then obtained while the left lung was inflated by increasing pressures. Since this procedure resulted in varying degrees of mediastinal distortion, with marked displacement of the heart to the right side, in the last three experiments a third series of venous pressure readings was obtained after opening the pericardium and holding the heart in its normal position with a silk suture passed through its apex.

RESULTS

Inflation of the lungs in the open chest preparation was regularly followed by an immediate increase in venous pressure. Within limits this increase in venous pressure was directly proportional to the degree of intratracheal pressure used. Furthermore, the curve of venous pressure response was a highly individual one for each animal studied so that the readings must be plotted separately. All of these changes have been observed by us in previous experiments,[7] and they constitute the control observations for the experiments reported in this paper.

When the venous pressure readings were repeated after resection of the right lung, the results were strikingly different. Under these conditions and with the same intratracheal pressures, venous pressure rose very little and when displacement of the heart was prevented the venous pressure change was even less. The failure of venous pressure to rise after resection of the right lung, however, was observed only within certain limits of intratracheal pressure. If intratracheal pressure was carried above these limits the right heart failed and then, as one would expect, the venous pressure rose rapidly until the circulation came to a standstill.

The results are shown graphically in Figs. 1 and 2.

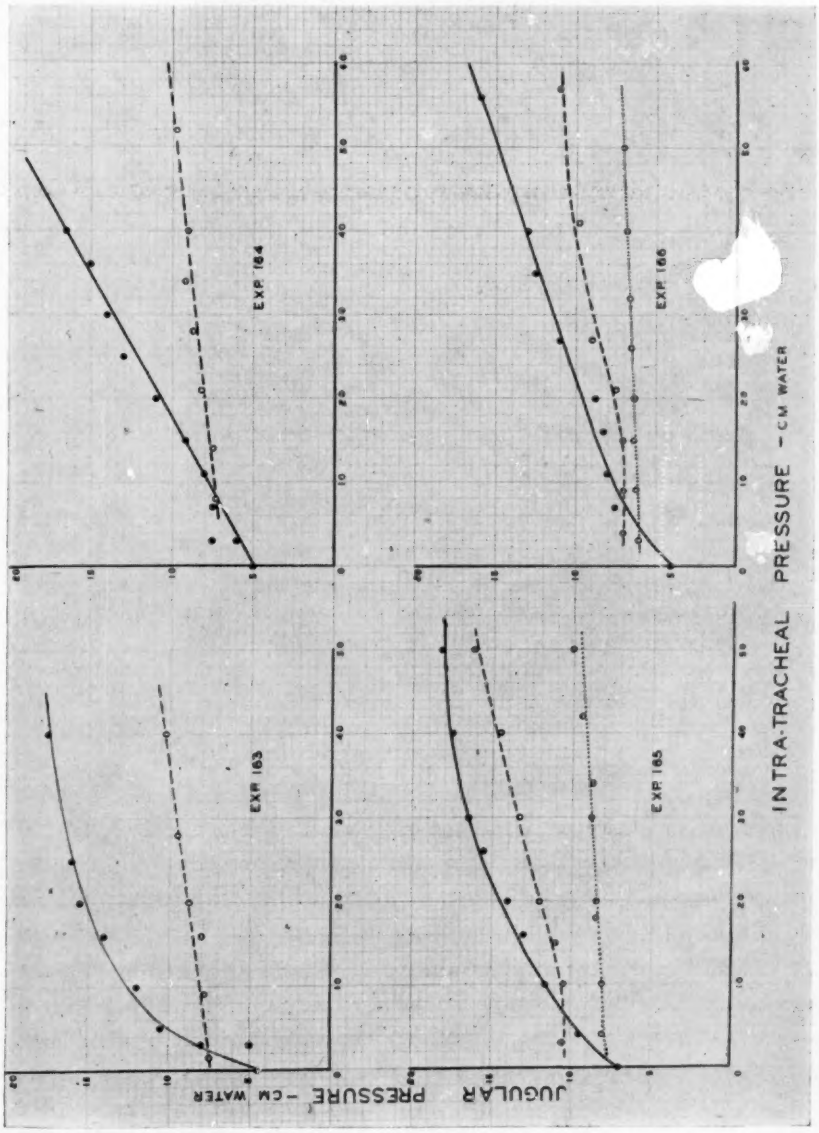

Fig. 1.—Venous pressure readings in the first four experiments plotted graphically against the intratracheal pressure. The solid line represents the changes in venous pressure when both lungs were present; broken line, the changes after resection of the right lung; and dotted line, the changes after resection of the right lung and immobilization of the heart. When both lungs were present, the rise in venous pressure was immediate and marked; after resection of the right lung, the rise was gradual and slight; and, finally, after resection of the right lung and immobilization of the heart, the rise was negligible.

DISCUSSION

Experimental studies have repeatedly shown that during gradual occlusion of the pulmonary artery there is no damming back of blood in the peripheral veins until heart failure occurs.[9, 10] Recently Mendlowitz[11] has demonstrated again that a normal dog's heart is capable of overcoming a very high degree of pulmonary arterial block without appreciable change in peripheral venous pressure. Our experiments were similar since inflation of the lungs at high pressures introduced a resistance to the pulmonary blood flow which was equivalent to blocking partially the main trunk of the pulmonary artery. When tamponade was prevented by resecting the right lung, there was no significant rise in

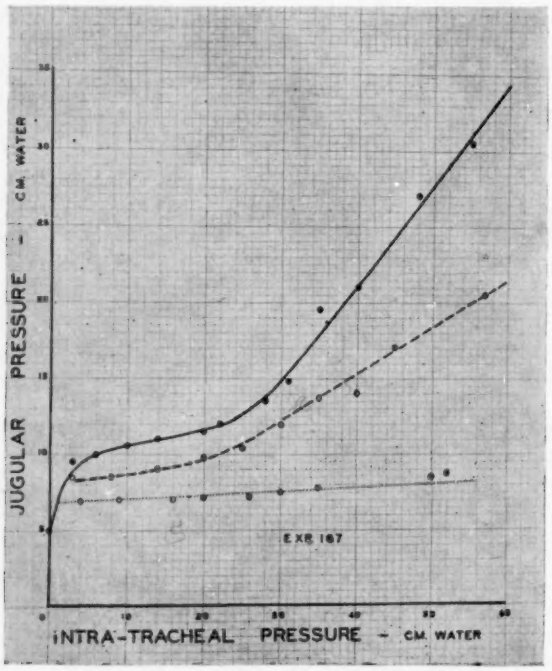

Fig. 2.—Venous pressure readings in the fifth experiment. In this animal venous pressure rose to an unusual height when both lungs were present (solid line), considerably less after the right lung had been removed (broken line), and almost none after the pericardium had been opened and heart held in normal position (dotted line).

venous pressure until the right heart failed. When both lungs were present, however, the venous pressure rose in direct proportion to the intratracheal pressure used. It is apparent, therefore, that the rise in venous pressure which accompanies inflation of the lungs cannot be attributed to the inability of the heart to overcome the increase in resistance in the pulmonary circulation which occurs at the same time.

Mediastinal emphysema was not observed in any of these experiments, although pressures well above those reported to cause it[3] were used, possibly because each pressure was maintained for only two minutes. If an early and overlooked alveolar rupture and emphysema did take

place, it cannot have been responsible for the rise in venous pressure, since the latter fell again as soon as the intratracheal pressure was lowered. Since the oxygen and carbon dioxide contents of the arterial blood were not studied, it is not known whether resection of the lung was followed by anoxia or accumulation of carbon dioxide due to impaired ventilation. Nevertheless, since the rise in venous pressure which accompanied inflation of both lungs did not occur after one had been resected, it cannot be attributed to anoxia or accumulation of carbon dioxide. It must be concluded, then, that a tamponade effect, caused by compression of the heart or great vessels between the expanding lungs, was responsible for the venous pressure rise when both lungs were present. When one lung was resected, there was no tamponade effect and consequently no rise in venous pressure.

The consistent finding of a high degree of individual variation in the type of venous pressure response, although its direction was always the same, is of interest. It seems probable that the shape of each animal's chest as well as age and general condition are determining factors.

Since the shape of the chest of a human being is very different from that of a dog, the tamponade effect produced by positive pressure anesthesia must differ in degree from that demonstrated in these experiments. It must, however, be similar and presumably shows similar individual variations. For this reason it cannot be said that one intratracheal pressure is safe and another dangerous. What is safe for one patient may be dangerous for another, and must vary for the same patient under different circumstances.

SUMMARY AND CONCLUSIONS

The jugular vein pressure of five anesthetized dogs was measured after opening the chest wide and inflating the lungs continuously at increasing pressures. The right lung was then resected by ligating and dividing the pedicle of each lobe separately, and the response of the venous pressure to similar intratracheal pressures was again observed. Finally, in three animals, a third set of venous pressure readings was obtained after the pericardium had been opened wide and the heart fixed in normal position by a suture through its apex.

The findings were as follows:

1. When both lungs were inflated at increasing intratracheal pressures, the jugular vein pressure rose in every experiment.

2. The rise in venous pressure was less abrupt and much less marked after resection of the right lung.

3. When, following resection of the right lung, the pericardium was opened and heart fixed in normal position, the rise in venous pressure did not occur until the right heart failed.

We believe these findings show conclusively that the decrease in cardiac output, which has been shown to accompany positive inflation

of the lungs in experimental animals, is due to compression of the heart and interference with its filling rather than to compression of the pulmonary vessels and interference with its emptying.

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OBSERVATIONS ON THE USE OF PROLONGED ANESTHETIC AGENTS IN UPPER ABDOMINAL INCISIONS

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IT HAS long been suspected that the limitation of respiratory excursions due to pain is an important factor in the relatively high incidence of pulmonary complications following operations on the upper abdomen. In his experiments Kahn has shown that stimulation of the central end of any intercostal nerve causes a reflex inhibition of respiration. Particularly is this true of the seventh to twelfth intercostal nerves. Similarly, stimulation of the peripheral branches, including those to the rectus abdominus muscle, inhibits respiration. Cutler and Hoerr have shown that this inhibition is greater than is perhaps generally realized, amounting to a 59 per cent depression of the mean vital capacity during the first few postoperative days.

The ordinary prophylactic measures, such as the avoidance of tight dressings, rebreathing with carbon dioxide, and frequent changes of position, employed to prevent or decrease the incidence of pulmonary complications, are effective only up to a certain point. To a considerable extent they are necessary only because the patient is either unable or unwilling to take a deep breath, to cough, or to move about in bed because of the pain arising from the surgical incision. It seems reasonable, therefore, that if the pain in the wound were alleviated sufficiently during the first few postoperative days, the patient would be more comfortable and the surgeon would have fewer pulmonary complications to contend with.

Many methods have been advocated to minimize the pain of surgical incisions. One approach has been directed at placing the incision in such a fashion as to interfere with as few sensory nerves as possible. Transverse incisions have accordingly been recommended by many surgeons.

As another approach to the problem, various types of anesthetic agents have been administered by a variety of methods and in a variety of locations. The use of anesthetic agents to alleviate the pain of surgical incisions over a prolonged period is by no means a new idea. Many years ago Crile,[1, 3] recommended the injection about the wound of quinine and urea hydrochloride in a 1/6 to 1/2 per cent solution. Although a satisfactory anesthesia lasting for several days resulted, the method was discarded because it produced fibrinous exudate with occasional suppuration at the sites of injection.

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

Capelle, a few years ago, recommended the continuous administration of novocain to overcome the pain in surgical wounds and to increase the postoperative vital capacity. He employed an ingenious apparatus, consisting of several large, thin, curved, hollow needles attached to a tube. These needles he inserted after closure of the peritoneum, in a fashion similar to the placement of retention sutures, thereby providing a tubular irrigation system for injecting the anesthetic agent as required. He found that the irritation from the needles was no more marked than that produced by wire retention sutures. Although this method may be effective in producing anesthesia in the wound over a prolonged period of time, it presents many obvious undesirable features.

Gius, impressed with Capelle's results, which showed a return of vital capacity from the usual 20 to 40 per cent of normal immediately after operation to 90 per cent of normal when the wound was anesthetized, adopted a paravertebral procaine block in the treatment of postoperative atelectasis. He reported the use of this paravertebral block of the lower thoracic and upper lumbar nerves in two children, who developed atelectasis following appendectomy. Both were relieved of their pain in the abdominal wound, and as a result could cough vigorously without distress. It was his impression that temporary abolishment of pain in the wound allowed hyperventilation of the lungs and effective coughing.

Although in our preliminary studies at the time of closure we injected an anesthetic in oil in the layers of the abdominal wall adjacent to the incision, we hesitated to use an amount sufficient to insure complete anesthesia of the wound. So we sought an agent which could be prepared in aqueous solution, and which would give prolonged anesthesia. On the basis of some observations by de Takats and Collins on the effectiveness of eucupin as a prolonged anesthetic, this material was selected. The solution used consisted of eucupin dihydrochloride 0.06 Gm., procaine hydrochloride 0.30 Gm. in Ringer's solution to make 30 c.c.* The procaine was added to give immediate anesthesia and to overcome the burning sensation that accompanies the injection of eucupin.

The effectiveness of local infiltration of eucupin-procaine solution was studied in a group of patients who had been submitted to gastric or biliary operations through vertical upper abdominal incisions. At the time of closure of the abdominal wound, while the patient was still under general anesthesia, the eucupin-procaine solution was injected locally about each side of the incision. No intradermal infiltration of the skin was carried out, but when retention sutures were used, infiltration was carried out about these as well. Although the amount injected was variable, it usually amounted to 50 c.c.

*The chemical used in these experiments was supplied by the Rare Chemical Co., Nepara Park, N. Y.

It was our clinical impression that these patients were more comfortable after operation and required less sedation than the average patient. But it is admittedly difficult to evaluate the amount of discomfort that patients experience after operation, for this varies according to the age, sex, and mental make-up of the individual. A record of the amount of sedation given, such as morphine, is unreliable, because sedatives may be prescribed for restlessness or to insure sleep, and not for pain in the wound.

One of the simplest and most reliable methods of determining the amount of pain following upper abdominal incisions is a record of the daily vital capacity. Cutler and Hoerr have shown that there is invariably a marked reduction in vital capacity after a high abdominal incision. Their figures were used by us as a control on the effectiveness of the method in increasing the respiratory excursions.

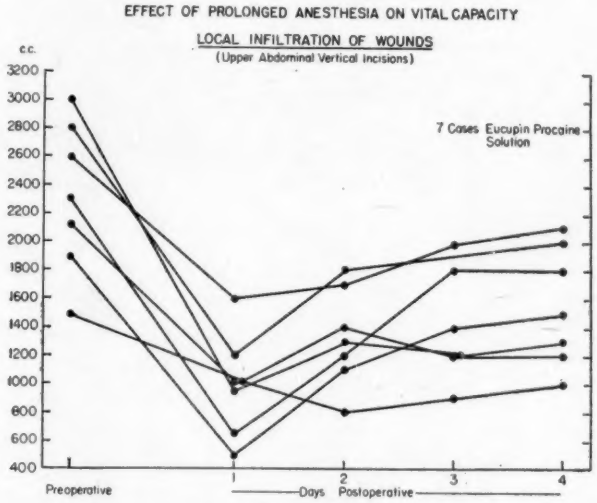

Fig. 1.—Graph of vital capacities before and after operation when eucupin-procaine solution was infiltrated locally.

In Fig. 1 is tabulated the vital capacity of patients whose upper abdominal wounds were infiltrated with eucupin-procaine solution. The vital capacity was recorded before and on succeeding days after operation. There was no significant variation as compared to the control cases.

Influenced by Bartlett's excellent report on the efficiency of intercostal nerve block for upper abdominal surgery, we studied the possibility of obtaining prolonged anesthesia by substituting an anesthetic in oil for novocain in intercostal nerve block. Burt and Gius, through experiments in animals, had shown that certain anesthetic agents in oil (neothesol) did not retard wound healing or increase the incidence of infection. Bartlett showed how the anatomical arrangement of the intercostal space, especially about the midaxillary line, lends itself to the application of nerve block anesthesia. The intercostal nerve in this location is in a closed compartment just beneath the inferior margin

of the rib between the external and internal intercostal muscles. This anatomical arrangement permits the use of relatively small amounts of an anesthetic solution with reasonable assurance of an effective nerve block. The anesthetic selected was eucupin base, 0.005 Gm.; ethyl aminobenzoate, 0.15 Gm.; benzyl alcohol, 0.25 Gm.; and sufficient oil of sweet almond to make 5 c.c.

The method of producing the intercostal block we employed was essentially that described by Bartlett. The side to be injected was elevated by a sandbag or pillow under the chest, and the arm was abducted (Fig. 2). It is helpful, especially in females with pendulous breasts or in obese individuals, in locating the inferior margin of the rib where the injection is to be given, to have the skin of the abdominal wall held

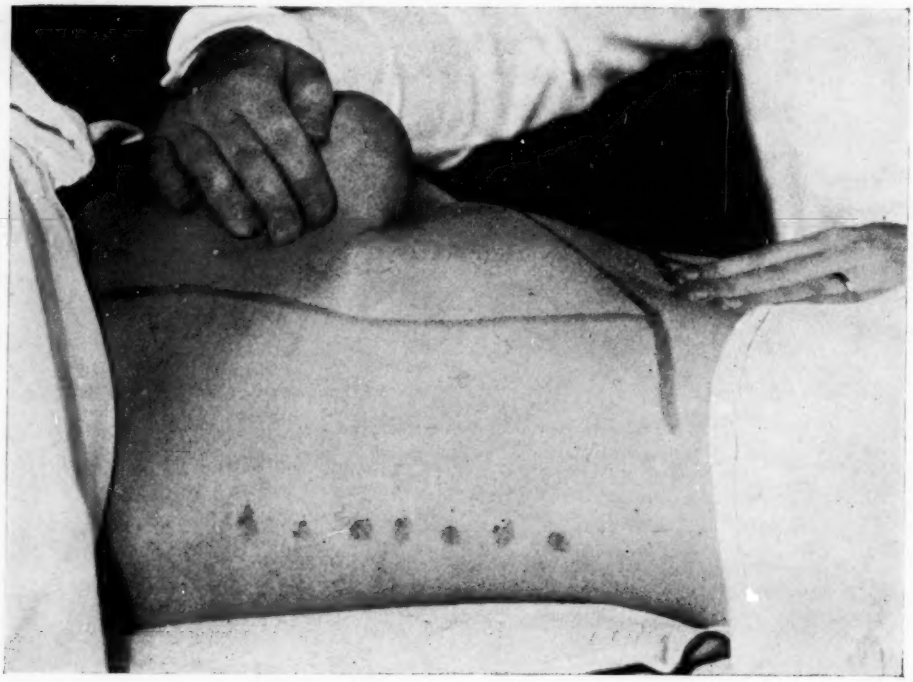

Fig. 2.—Location of points of injection for intercostal anesthesia.

taut by an assistant. The lateral chest wall was well elevated to permit injection in the midaxillary line or slightly posterior, because in the usual position on the operating table we have found that there is a tendency for the injection to be made too far forward on the chest wall to assure a satisfactory block anesthesia. After the skin is suitably prepared and the anesthetic in oil has been warmed, the injection is made with a No. 19 needle. One can feel the needle pass beneath the inferior margin of the rib and through the fascia covering the external intercostal muscle (Fig. 3). The point of the needle should then be in the compartment between the two intercostal muscles adjacent to the intercostal nerve, but to make sure that the point of the needle has not

entered the pleural cavity repeated attempts are made to withdraw the plunger. The injections were usually started at the eleventh rib and continued upward to include all the intercostal nerves as far as the fifth or sixth, depending upon how high the upper abdominal incision was to be carried.

Varying amounts of eucupin solution in oil, from 1.5 to 5 c.c., were injected into the individual intercostal spaces. Effective nerve block probably does not depend so much upon the amount of anesthetic in oil which is used as upon accurate injection of the solution in relation to the intercostal nerves. For example, the best result we obtained came after an injection of only 1.5 c.c. into each intercostal space. For right rectus incisions in procedures on the biliary system, we have used the block anesthesia on one side only. However, if the incision was made near the midline and retention sutures were used, bilateral nerve block was carried out, as it also was for midline incisions or those slightly to the left of the midline.

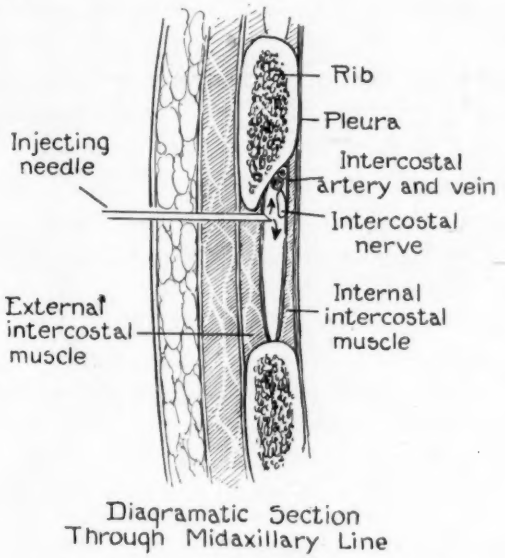

Fig. 3.—Illustration of point of injection, the closed intercostal space (after Bartlett).

Since the introduction of the intercostal block is not without some discomfort to the patient, we now prefer to introduce it after the patient is asleep or at the end of the operation. However, until the technique was acquired, we carried out blocking before the induction of general anesthesia. This insured complete anesthesia of the field, for the effectiveness of the anesthesia over the upper abdomen could be checked by needle prick, and if the anesthesia was not complete, the injection could be repeated as necessary. In addition, this permitted us to test the completeness and effectiveness of the nerve block by opening the abdomen without additional anesthesia. In these instances we noted a tendency toward increased bleeding in the wound. Except for the

peritoneum, the abdominal wall was, as a rule, anesthetized satisfactorily. The operation was then continued under general anesthesia. The induction of the block anesthesia in the conscious patient also permitted studies of vital capacity to determine whether interference with the motor innervation in the involved intercostal or upper abdominal muscles lowered the vital capacity. No significant change in the vital capacity was found.

One question which naturally arises is whether or not the introduction of an anesthetic in oil containing benzyl alcohol produces an undesirable reaction in the adjacent pleura or the pleural cavity, should it be accidentally injected therein. Although we have not been able to detect any noteworthy reactions in patients, some local reaction must occur judging from observations in animals.

Eucupin solution in oil was injected intercostally in dogs, following a technique similar to that used in patients. Two cubic centimeters of anesthetic in oil were injected into four intercostal spaces. This is a large quantity in relation to the thin intercostal spaces in dogs. The depth of the site of the injection was more difficult to control in the animals than in human beings. Since we were primarily interested in the early reaction of this material, the animals were sacrificed one, two, seven, and fourteen days after the injection. Further studies on the effect of this material are in progress.

Invariably there was a noticeable reaction about the pleura in the area injected. Also there was usually a small amount of fluid in the chest and a deposit of fibrin on the surface of the lung opposite the injection. In one animal 8 c.c. of eucupin solution in oil were injected directly into the pleural cavity, and the animal was sacrificed after one week. At autopsy a small amount of thin, brown fluid was found in the chest, a minimal amount of reaction compared to what might have been expected. The accidental injection of eucupin solution in oil directly into the pleural space in patients would probably be without consequence.

RESULTS

Like any attempt at infiltration anesthesia, the results are not uniformly successful. This can be expected, especially if a small amount of solution is injected. Furthermore, as previously stated, it is difficult to evaluate in some patients the amount of discomfort after operation. Some nervous, apprehensive individuals, despite the fact that they did not require much sedation for relief of their pain, did not cooperate when vital capacity determinations were made.

For purposes of analysis we have divided the instances in which eucupin solution in oil was used as an intercostal nerve block into two groups: biliary operations and gastric resections. The former group was made up of 10 women, in 8 of whom choledochostomy in addition to cholecystectomy was carried out. In 9 the block included the sixth

to the eleventh intercostal space in the midaxillary line on the right side. Only in 1 patient was a bilateral block produced.

Fig. 4 presents the vital capacities of these patients before operation and on the four days immediately following operation contrasted to those of 48 women on whom similar operations were carried out without intercostal block anesthesia. The majority of the patients had a vital capacity greater than the median vital capacity attained by any 1 of the 48 in the control group. The vital capacity of 1 female quite remarkably was not below 3,000 c.c. after operation. Six of the 10 were above the maximum on the first postoperative day, while 1 equalled the maximum and 3 were below.

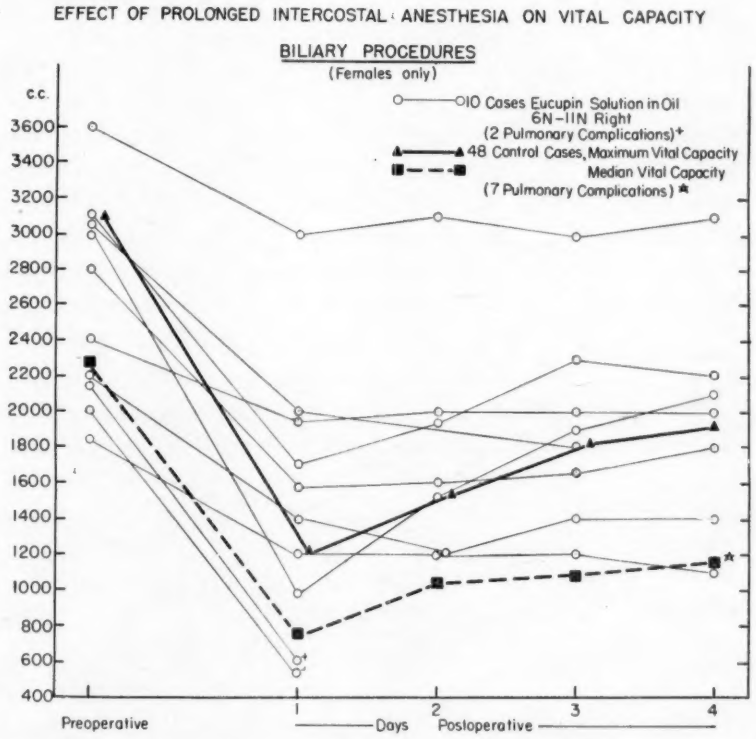

Fig. 4.—Comparison of vital capacities of 48 control cases before and after biliary operations with 10 cases in which eucupin solution in oil was injected intercostally on the right side.

Two patients, 1 with a bilateral block, complained of pain immediately after recovery from the general anesthesia, required morphine in repeated doses, and showed signs of pulmonary atelectasis within twenty-four hours of operation. Further vital capacity readings were not taken on these 2 patients. As far as we could determine, the block had failed and had no effect upon the pain from the surgical incision.

An x-ray of the chest, taken eight days after operation in the patient with bilateral block, showed fairly marked clouding, together with some fluid at the right base but no displacement of the heart or trachea. The left side was clear. A diagnosis of bronchopneumonia and pleural

effusion on the right side was made. She had a sustained elevation in temperature for two weeks, which gradually returned to normal.

An x-ray of the chest of the second patient on the third day after operation showed clouding of the right base, suggesting a small amount of fluid obscuring the diaphragm and costophrenic angle. The lungs elsewhere were clear. This patient's recovery was not interrupted, and she was discharged on the thirteenth day after operation.

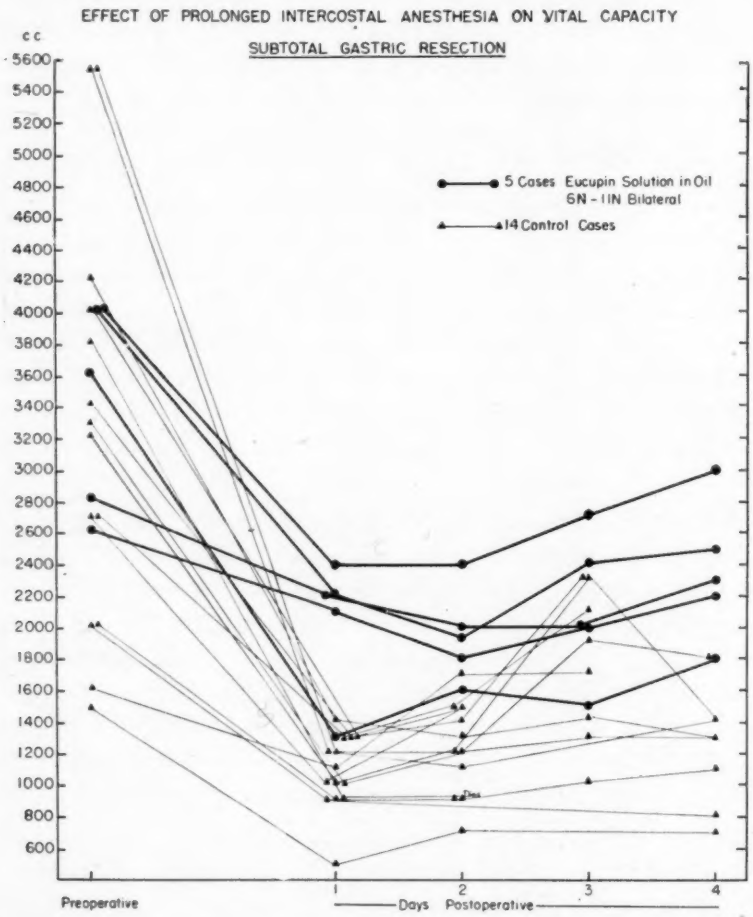

Fig. 5.—Comparison of vital capacities of 14 control cases before and after gastric resection with 5 cases in which eucupin solution in oil was injected intercostally on both sides.

The question may be raised of whether or not the eucupin solution in oil was accidentally injected into the chest. It is our opinion that the intercostal nerve block was not primarily responsible for the patients' pulmonary complications. Obviously, we cannot say that we have been able to decrease the incidence of pulmonary complications in this small series of cases; although it is admittedly true that these two patients who developed pulmonary complications did not have a satisfactory block, as shown by their evident distress immediately after operation.

Fig. 5 is a comparison of 5 patients submitted to subtotal gastric resection, when eucupin solution in oil was injected bilaterally to produce intercostal block, with 14 in which it was not used. The majority of these were men. In general, it is difficult to compare the vital capacity readings of men and women. While the readings of the men may be as low as those of the women on the first day, the former return to normal much more rapidly. As shown in the chart, the vital capacity in the control cases was abruptly lowered to 1,400 c.c. or below, regardless of the preoperative reading, which in two instances was as much as 5,500 c.c. There was some increase on the second postoperative day, and a sustained increase on the third day. In 4 of the 5 patients with nerve block, the fall of the postoperative vital capacity was not nearly so marked and the vital capacity readings averaged from 2,100 to 2,400 c.c. There was some evidence that the anesthesia was not as effective on the second day, in that the vital capacity showed a trend to a lower level then, followed by a sustained rise. One patient after radical resection of the Polya type, including fundusectomy, showed a vital capacity on the first two postoperative days comparable to the maximum for the control group. There were no pulmonary complications in the patients in whom the block was used, while there were five in the control group. At least 2 of the patients having gastric resection had no morphine after operation.

If the patient has a decrease in the usual distress in the wound following operation, as shown by an increase in vital capacity, one should be able to demonstrate persistent anesthesia of the abdominal wall. In a few patients we found a spotty, persistent anesthesia the day following operation, but in the majority sensation had returned to the skin in the blocked area by the time of the testing. Despite the lack of local anesthesia, the patients did not have any significant amount of pain. This observation coincides with that of de Takats, who has pointed out that with eucupin injection a prolonged period of analgesia follows the period of local anesthesia.

One patient who complained of pain on the first day after operation stated that the pain was located in the left epigastrium below the lower angle of the incision outside the zone supplied by the block. This "migration of pain" after anesthetization of a painful area has been described by Weiss and Davis, who suggested that after alleviation of pain by local infiltration of the skin with novocain, the pain may recur in a corresponding segment which is more sensitive. The observer must be aware of this possible manifestation of referred pain.

Whether or not these patients will show evidence of a chemical neuritis or an intercostal neuralgia, as sometimes follows paravertebral alcohol injection, remains to be seen. Only 2 patients of the entire group have complained of any discomfort at the point of injection and this was not particularly noteworthy.

Although the number of patients here reported having intercostal nerve block with an anesthetic in oil is small, the method seems to be of value when one considers the marked elevation in vital capacity during the early days after operation in the majority of instances. Whether the lower incidence of pulmonary complications is real or fortuitous remains to be seen. Clinically, and particularly from the point of view of the patient, the procedure appears to be worth while. Further investigations are in progress.

CONCLUSIONS

1. The block of the sixth to the eleventh intercostal nerves with eucupin solution in oil decreases the postoperative pain of upper abdominal incisions, as demonstrated by vital capacity measurement.

2. The question of whether intercostal nerve block with eucupin solution in oil will decrease the incidence of postoperative pulmonary complications can be answered only by further observations in a larger series of cases. The procedure seems to have merit and warrants further investigation and clinical trial.

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BENIGN STRICTURE OF THE BILE DUCTS TREATED WITH A VITALLIUM TUBE

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BENIGN strictures of the bile ducts may follow injury during cholecystectomy, ulcerations from stones, or septic cholangeitis. They are always a difficult situation to manage and if very extensive may present an insoluble problem. Two general principles have been used in their operative repair; either an attempt to restore the lumen of the damaged duct or transplantation of its proximal end into the intestinal tract. Restoration of the duct has been done by (1) dilatation or division of the stricture, (2) plastic repair usually by the Heineke-Mikulicz principle, (3) excision of the stricture with end-to-end anastomosis of the duct, or (4) the use of a rubber tube to bridge the gap between the ends of the duct. These operations have the advantage of retaining the action of the sphincter of Oddi and so prevent ascending infection. If either plastic repair or end-to-end anastomosis of the duct can be done without tension on the suture line, the results are often satisfactory. These are the best procedures for the management of the less severe strictures.

The proximal end of the common or hepatic duct has been transplanted into the stomach, duodenum, or jejunum. An external biliary fistula has been utilized for transplantation into the intestine. Finally, indirect transplantation has been done with a tube from the hepatic duct to the intestine. Of these hepaticoduodenostomy has been the most frequently employed, but all have the possible danger of cholangeitis due to infection ascending from the intestinal tract into the biliary system. They also are prone to restricture at the site of the anastomosis.

This report deals with the use of a buried vitallium tube to repair extensive strictures of the ducts. The method was thought of in connection with the patient in Case 1, who on two occasions was perfectly well as long as a T-tube was in the duct but who had stricture formation and a return of symptoms after removal of the tube. The use of a buried tube left in place permanently was an obvious solution if one could be found that was satisfactory. The work on bones and joints had shown that vitallium was practically inert in the tissues probably from absence of electrolysis. It was selected for the purpose* in the hope that it would

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

*The Austenal Laboratories, New York City, have been most helpful in making this and other tubes. I have appreciated their cooperation.

be tolerated well enough to keep the strictured duct patent. When the vitallium tube relieved the symptoms of cholangeitis and biliary obstruction in the first patient, we were encouraged to suggest its use in two other patients. These are reported.

CASE 1.—M. T. (No. 151537) was admitted March 29, 1939. This 30-year-old woman had had a cholecystectomy elsewhere in July, 1937. She was told that the common bile duct was explored and that several small stones were removed from it. Recovery was slow and she was in the hospital five weeks. Soon after healing of the wound she began having attacks of epigastric and interscapular pain associated with nausea, vomiting, chills, fever, and jaundice.

A second operation was done elsewhere in May, 1938, at which time she was told a stone was removed from the common bile duct. A catheter drained bile after this operation and she felt perfectly well until after its removal. Then the symptoms of pain, nausea, vomiting, chills, fever, and jaundice returned. Intense itching, clay colored stools, and dark urine were occasionally observed.

In the past she has had five normal pregnancies and a laparotomy four years ago for uterine suspension.

Physical examination revealed a well-developed, moderately well nourished woman with sallow skin, icteric sclerae, three well-healed abdominal scars, and a liver palpable just below the costal margin. All other physical findings were within normal limits.

Laboratory studies gave the following results: *Blood:* R.B.C., 4,200,000; W.B.C., 7,500; Hgb., 12.5 Gm.; differential normal; Wassermann negative; bleeding time, 2½ minutes; clotting time, 3 minutes; prothrombin time, normal; fragility of R.B.C., normal. *Blood Chemistry:* N.P.N., 33; sugar, 70; icterus index, 15; albumin, 2.85 per cent; globulin, 2.87 per cent; total protein, 6.8 per cent; cholesterol, 250 mg. *Urine:* Specific gravity, 1.025; alkaline; albumin, 0; sugar, 0; acetone, 0; guaiac, negative; mic. 3 to 5 W.B.C. per field; foam test, trace of bile; $HgCl_2$ test negative. Stool guaiac negative, no parasites found. Duodenal drainage shows numerous cholesterol crystals. The glucose tolerance test shows a normal curve. Agglutination of the blood was found in 1:80 dilution of *Brucella abortus* and *Br. melitensis.* No agglutination for *Bacillus typhosis* or *B. paratyphosis.* X-ray of the gall bladder region showed no opaque calculi.

A diagnosis of stricture of the common bile duct with cholangeitis was made.

At operation, April 5, 1939, the gastrohepatic ligament was exposed, the portal vein and hepatic artery were isolated from dense scar tissue, but the bile duct could not be found. At this stage a small spot of bile was seen up under the liver and on tracing its source it was found to be coming from a threadlike structure in scar tissue. This was the remnant of the common duct. Traced upward it led to a dilated hepatic duct containing bile under pressure, gravel, and two stones. Below it led to the stump of the common duct which protruded about ¼ inch above the pancreas. The two ends were separated by a gap of about 1½ inches (Fig. 1, *1*), but due to unusual mobility of the pancreas and duodenum it was possible to join them by an end-to-end anastomosis over a T-tube (Fig. 1, *1a*). Recovery was uneventful.

On May 18, 1939, six weeks after operation, the duct system was visualized by x-ray after injection of opaque media and found to be patent so the T-tube was removed. She was well for three months, but then nausea, vomiting, chills, fever, and jaundice returned. At this time it was found that she was pregnant and when careful regulation failed to influence her symptoms the pregnancy was interrupted for it was an obvious menace to her.

The attacks of cholangeitis grew worse in spite of all treatment until she was having a daily chill with temperature of 40° C. (104° F.). It was apparent she could not survive in this condition, yet it was thought that there was too little duct left for further attempts at plastic repair. It was decided to intubate the duct permanently.

On Feb. 26, 1940, the fourth operation on the biliary ducts was done. After freeing dense adhesions the dilated stump of the hepatic duct was exposed and a stricture found at the point of former anastomosis (Fig. 1, *2*). There was one stone

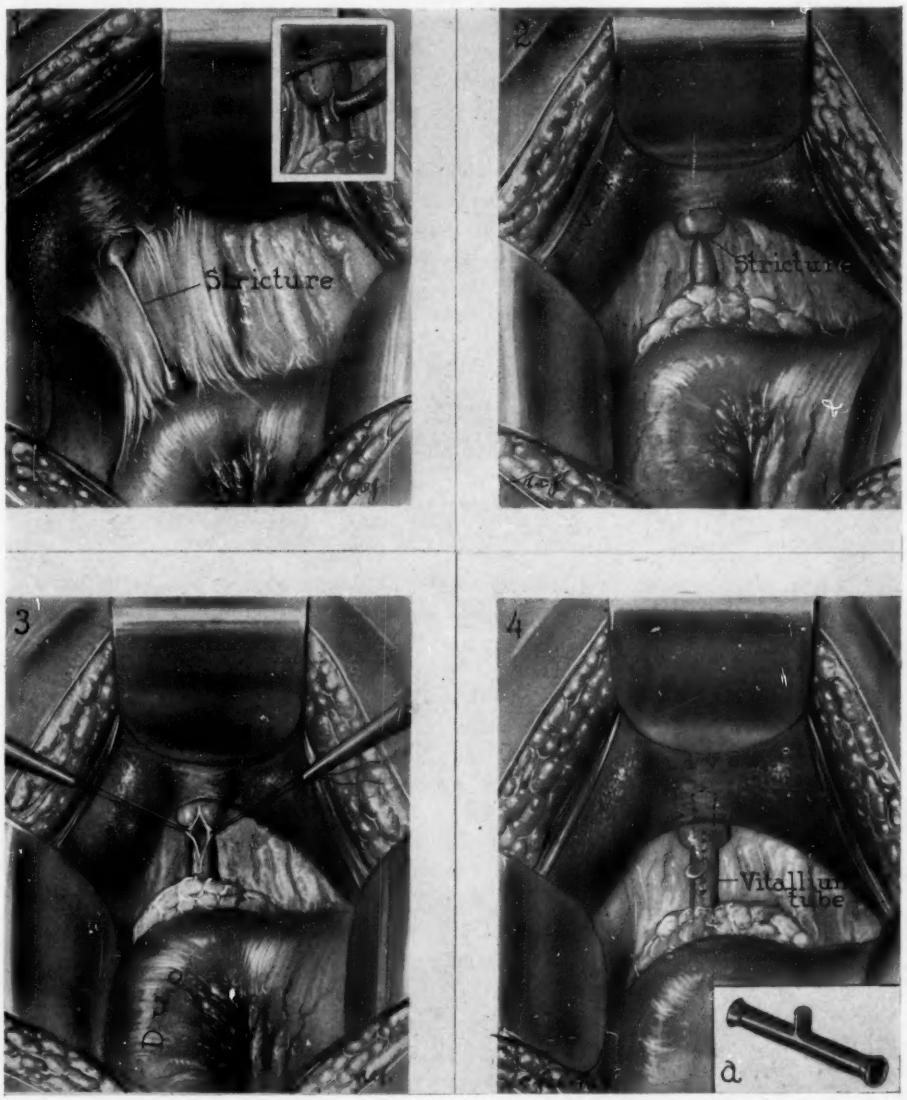

Fig. 1.—*1*, The stricture of the bile ducts in Case 1 extended from the upper hepatic duct to the lower common bile duct. For clarity it is shown isolated but in reality it was buried in dense scar tissue since this was the third operation on the biliary tract; *a* shows the method of repair by end-to-end anastomosis over a T-tube. This was made possible by exceptional mobility of the duodenum and pancreas. *2*, Ten months later the anastomosis had strictured down to a small opening but the ends of the duct were held together by scar tissue. *3*, The ducts were opened without dividing their attachment to one another. *4*, The vitallium tube was slipped into the ducts and their anterior walls were closed over it. The flange protruded through the suture line; *a*, drawing of the vitallium tube showing the thickening of the ends and the central flange which acts as an anchor.

removed from the duct above the stricture. The vitallium tube was inserted into the duct which was closed about it (Fig. 1, *2* and *3*). Recovery was uneventful.

Follow-up examinations at monthly intervals for one year have shown the patient to be in good condition. On one occasion she developed indigestion and diarrhea, possibly from too much sodium taurocholate for when this drug was eliminated the symptoms subsided. She is now well.

CASE 2.—B. L. (No. 168083), was admitted Aug. 1, 1940. Two years before this 37-year-old married white woman had had a cholecystectomy at another hospital because of symptoms of right upper quadrant abdominal pain radiating to the back, nausea, vomiting, and jaundice. The wound drained for three months. Six months postoperatively she began having recurrent attacks of right upper quadrant abdominal pain more severe than before the operation. These have been associated with nausea, vomiting, chills, fever, jaundice, clay-colored stools, and dark urine. Recently the jaundice has been constant though it fades somewhat between attacks.

The physical examination, except for jaundice and a healed abdominal scar, was negative. Temperature was 37° C.; the pulse, 80; the respirations, 20; and blood pressure, 120/76. Laboratory examinations showed bile in the urine; clay colored stool; negative Wassermann; blood N.P.N., 34 mg. per cent; sugar, 90; icterus index, 48; amylase, 100; prothrombin time, normal (26 seconds). X-ray examination of the abdomen showed no opaque calculi.

A diagnosis of residual common duct stone or stricture of the common duct was made and operation was advised.

Operation (Aug. 5, 1940, Dr. T. B. Jones).—The abdomen was opened through an upper right paramedian incision. Numerous adhesions were freed to expose the stomach adherent to the gall bladder bed. There was a broad band of tissue binding the stomach to the region of the cystic duct. When this was divided, bile escaped and a small fistula was demonstrated between the stump of the cystic duct and the stomach. The gastric opening of this was inverted with silk. The hepatic artery was anomalous, being located to the right and posterior to the common duct. The bile duct was a fibrous cord from just distal to the hepatic ducts down to a point 1.5 cm. above the duodenum. The stricture was considered to be too extensive for a satisfactory plastic repair. Consequently a vitallium tube was inserted into the proximal part of the duct just below the bifurcation of the hepatic ducts and was held in place with C silk sutures. The lower part of the tube was sutured in place into the distal end of the common duct. But the two ends of the duct could not be joined over the tube. A cigarette drain was inserted through the right flank into the gall bladder bed some distance from the common duct and the wound of exploration was closed with silk sutures.

The patient made a smooth postoperative recovery. The icterus index was 36 two days after operation and fell to 14 five days later after which the clinical signs of jaundice disappeared. She was discharged from the hospital on the eighteenth postoperative day in good condition.

Follow-up examinations at monthly intervals revealed her condition to be very good until five months after operation at which time she complained of gas, diarrhea, and bulky, "frothy" stools. She had gained 16 kg. in weight and was eating excessively because her appetite was "tremendous." A blood icterus index was 8; cholesterol, 283; and amylase, 160. A low fat diet and sodium taurocholate, 0.5 Gm. b.i.d., was prescribed. Two weeks later, Jan. 22, 1941, she had jaundice with itching of the skin and an icterus index of 24. There was no pain, chills, fever, or vomiting associated with this. On Jan. 29 the jaundice was increased with an icterus index of 36. By Feb. 5 the icterus index was 50 so she was readmitted to the hospital for operation.

Operation (Feb. 8, 1941, Dr. H. E. Pearse).—Dense adhesions were freed to expose a strictured stump of the common hepatic duct only 0.5 cm. of which was patent below the bifurcation into the right and left hepatic ducts. A stump of scar tissue protruded from beneath the duodenum, and by tracing this down, a patent common duct was defined. This was confirmed by making a small opening in the duodenum to inspect the ampulla with a probe in place. The vitallium tube had pulled out of the ducts and lay free beneath the pancreas and duodenum.

The two ends of the bile ducts approached one another at an acute angle so that when a T-tube was inserted into them it buckled in the middle. There was so much scar in the stump of the hepatic duct that it appeared probable that a hepaticoduodenostomy would result in stricture formation. Consequently the vitallium tube was reinserted and the ends of the ducts were sutured. The duct ends could only be approximated on their posterior wall by the use of some tension. The flange on the tube protruded between the ends on the anterior surface. The patient stood the operation well and is making a satisfactory recovery.

The following résumé was obtained through the courtesy of Dr. Howard M. Clute, of Boston, who operated upon the patient.

CASE 3.—Mrs. M. L. (No. 2488).

1. Cholecystectomy for gallstones was performed elsewhere sixteen months before. Hemorrhage occurred from the cystic artery. A clamp was hurriedly placed and left in place 24°. It apparently included the uppermost portion of the common duct in its grasp.

2. Common duct was explored four months before elsewhere because of attacks of pain, fever, chills, and jaundice. No stones were found. Stricture was not found.

3. At operation (Dr. Clute) on July 27, 1938, a stricture, almost complete, very high in common duct was found. The stricture was incised longitudinally, and a T-tube drain placed in it. The patient was well for five months with the tube in place. It was then pulled out. Soon after that attacks of pain, chills, fever, and jaundice began again.

4. At operation (Dr. Clute) on April 14, 1939, with great difficulty the strictured common duct was exposed. There was about one-eighth inch of common hepatic duct present. The duodenum was freed, and a hepaticoduodenostomy was done. A ring of fibrous tissue about the common hepatic duct opening made us fearful that the new opening might contract and obstruct. After six or seven months this occurred, and her old attacks of pain, chills, fever, and jaundice returned.

5. At operation (Dr. Clute) on Nov. 29, 1940, the common duct was again exposed and the duodenum was cut free from its anastomosis to the common hepatic duct. The anastomosis had diminished to pin-point size. The opening in the duodenum was closed. The common hepatic duct was now found lying somewhat in liver tissue and consisting really of only a ring of firm fibrous scar tissue. In the duct was much detritus and many tiny black gallstones. The end of the duct was enlarged and the trumpet-shaped end of a vitallium tube was inserted in it (Fig. 2) and held securely with two silk sutures. The distal end of the tube was placed in the common bile duct about one inch of which was absent. A jejunostomy was made for postoperative feeding. Recovery was entirely uneventful, her highest temperature being 99.4° the day after operation.

At last follow-up visit, Jan. 20, 1941, she was entirely well.

DISCUSSION

The literature has been studied, but it does not appear necessary to review it here. Those interested will find that Kehr[1] reports the earlier

work and that the review of Eliot[2] gives a good bibliography of recent articles on the subject.

The implantation of a buried tube to repair strictures of the bile ducts is not new for it has been used to bridge temporarily an irreparable gap or to hold open an anastomosis. These tubes were tied in place in the hope that they would loosen and pass spontaneously after restoration of the duct. When the use of a permanently buried tube was first considered, it was thought that rubber would be unsatisfactory for it

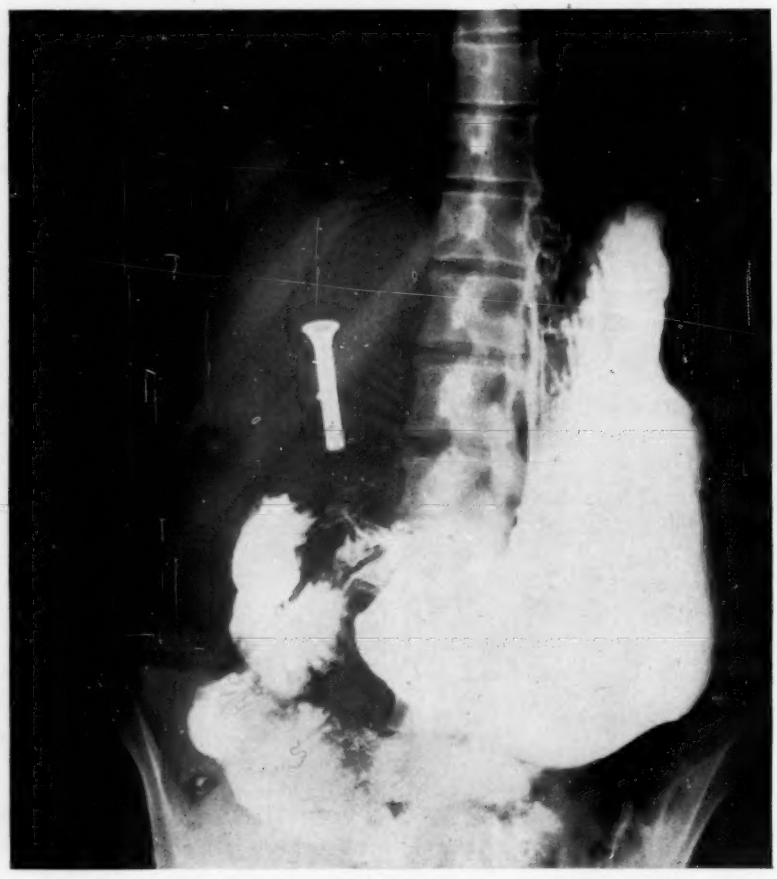

Fig. 2.—A vitallium tube in place in the bile ducts shown in relation to the stomach which is filled with barium. The bell-shaped upper end was used by Dr. Clute in Case 3 to collect bile from the right and left hepatic ducts for the patient's stricture was just below their bifurcation. A Y-shaped tube has also been suggested for this purpose.

would rot. Judd[3] reports a case of a rubber tube being in place for six years and Brooks[4] tells me of a case of his with a T-tube still in the duct after six years. Yet these are exceptions to the general rule that rubber begins to deteriorate in a year or so.

Vitallium has been shown[5, 6] to be the best tolerated of any metal in the tissues. It was also thought to be superior to glass or a plastic. The strength, lack of electrolysis, and lack of tissue irritation, all recommend vitallium for this purpose. The tubes were made with an internal

diameter of 5 mm. and a length of 4 cm. The ends were flared slightly to give added thickness at the edge to prevent pressure erosion. A flange was put in the center as an anchor. This protrudes through the wall of the duct and prevents the tube from slipping up or down. There have been several modifications of the anchoring device suggested, but so far none have appeared better than this simple flange. In Case 3 Clute wanted a tube to drain the two hepatic ducts for the patient had a high stricture. He obtained a Y-shaped tube and also one with a bell-shaped dilatation of one end. The latter was used and is shown in Fig. 2.

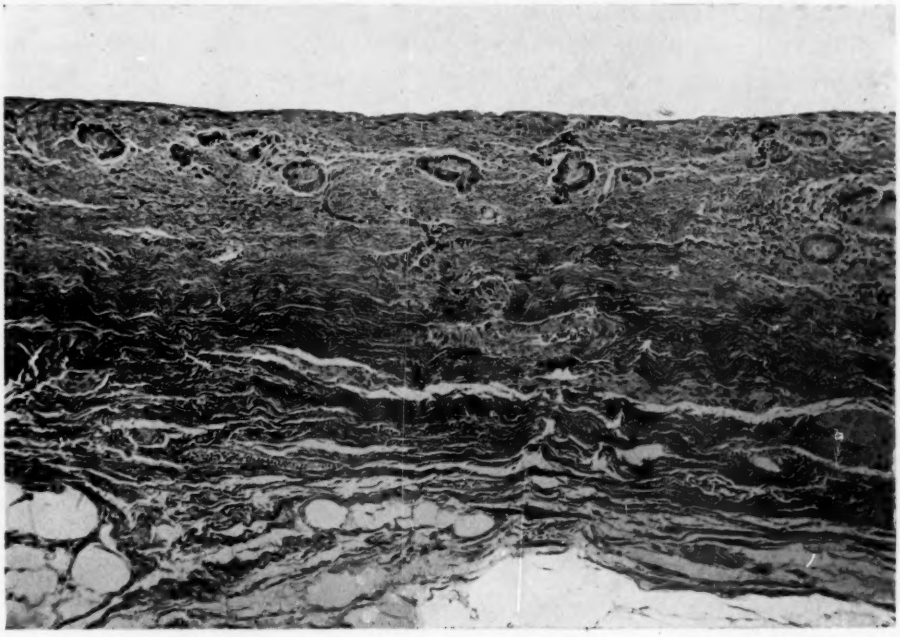

Fig. 3.—A vitallium tube has been in this dog's common bile duct for two months. The suction shows little change in the mucosal lining or in the wall of the duct.

It is felt that these tubes of vitallium should only be used in extensive biliary strictures which appear irreparable by other means for the hazards of this permanent intubation of the ducts cannot now be fully estimated. The patient in Case 1 has gone one year after operation without difficulty. Experiments in dogs have shown that the tube remains patent for months, the metal retains its luster, there is no deposition of pigment or salts on it, and the mucosa lining the duct is not seriously eroded (Fig. 3). But these experiments are only of a few months' duration and it will require years for the final answer. The same is true of experiments to test the effect of bile on the metal. Dr. Robert Sewell in our laboratory has had strips of vitallium suspended in human bile for several months without any indication of erosion of the metal.

It would appear likely that the greatest value of permanent implantation of a vitallium tube into the bile ducts will be to hold open a strictured area such as existed in Case 1. Its value is problematical if a gap is to be bridged between the ends of the duct. Here the tube may slip out as happened in Case 2. In such a situation it may be possible to free the duodenum and pancreas in order to gain mobility of the distal end of the common duct. The duodenum, pancreas, and duct could then be brought up near the hepatic duct. This was suggested by Dr. Earle Mahoney and was attempted at our second operation in Case 2 but was only partially successful due to scar tissue binding the undersurface of the pancreas. Normally there exists a good cleavage plane which might permit this maneuver.

The real test of the vitallium tube will be its use in clinical cases of severe biliary stricture which have not been corrected by previous operations. Here the surgeon has little to offer the patient so that prospect of benefit from the tube is sufficient to warrant its trial.*

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*The cases reported above have remained well to date (June 18, 1941). Other cases have been operated upon, here and elsewhere, with satisfactory results confirming the conclusions drawn in this report.

ADHESIONS FROM HOT LAPAROTOMY PADS

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THE proper temperature for moist laparotomy pads applied to the abdominal viscera has not been extensively studied. Most writers have urged that they be kept warm enough to avoid cooling the peritoneum. A cursory search through the voluminous literature on adhesions revealed that only Lamson[1, 2] and Benjamin[3] have mentioned the obvious fact that excessively hot pads may injure the peritoneum and cause postoperative adhesions. Since it is a common occurrence for the surgeon to be handed a pad that is literally too hot to handle, a more careful study is indicated of temperatures that cause thermal injury to the serosa.

MATERIAL AND METHODS

The effect of hot laparotomy pads on the peritoneum was studied in a series of twenty-six dogs. After laparotomy through a rectus incision several feet of small intestine, a portion of omentum, and in some cases the spleen were delivered into the wound. Pads were removed from large beakers of sterile water at known temperature, wrung out, and applied to these viscera for at least two minutes. Care was taken to keep drying and mechanical trauma at a minimum. The wounds were closed and the animals were sacrificed after intervals of two to forty-nine days postoperatively.

At post-mortem the viscera subjected to hot laparotomy pads were examined for the presence of adhesions. Microscopic studies were made of involved areas. An attempt was made in other experiments to determine the thermal death point of serosal cells in spread preparations of omentum and mesentery supravitally stained with neutral red and methylene blue. In another study a comparison was made between the temperature of moist laparotomy pads and the sensation induced in the surgeon holding these pads in his gloved hands.

GROSS FINDINGS

The effect of hot laparotomy pads on the production of adhesions in 26 dogs is summarized in Table I. In the case of 5 control animals in which the pads were applied at approximately body temperature (35 to 40° C.) no adhesions were present. In 6 dogs after laparotomy pads at 45° C., 1 had no peritoneal injury, 4 had moderate and 1 marked

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

TABLE I

NUMBER AND DEGREE OF ADHESIONS PRODUCED IN 26 DOGS BY APPLICATION OF HOT LAPAROTOMY PADS

TEMPERATURE (C.)	DOGS	ADHESIONS		
		SLIGHT	MODERATE	MARKED
35-40°	5	0	0	0
45°	6	0	4	1
50°	8	1	1	6
55-65°	7	2	1	4

adhesions. Moderate adhesions consisted of several bands or a single loop firmly adherent. Marked adhesions involved many loops of intestine. Of 8 dogs after laparotomy pads at 50° C., 6 showed massive adhesions, 1 moderate and 1 slight adhesions. After higher temperatures, 55 to 65° C., 4 of 7 dogs had massive adhesions, 1 died of peritonitis, and 2 showed a single adhesive band on the ileum. During operation intense hyperemia and in some cases punctate subserosal hemorrhages were noted to result from excessively hot pads.

The density and firmness of the adhesions varied with their duration and also with the extent of peritoneal damage. The moderate adhesions from 45° pads were largely thin bands while those from 50° and above consisted of broadly approximated bowel-to-bowel adhesions. As early as ten days postoperatively these broad adhesions could scarcely be pulled apart without tearing the bowel wall. Attachment of the omentum to the involved areas was often extensive but rarely firm.

Apparently the omentum and the peritoneal suture line were the only structures to take part in the formation of adhesions regardless of their exposure to hot pads. The parietal peritoneum and other portions of the gastrointestinal tract not subjected to thermal trauma did not become involved. Hot pads to the spleen produced fibrinous and fibrous thickening on its surface, omental attachments, but no adhesions to the neighboring stomach, colon, or parietal peritoneum.

MICROSCOPIC OBSERVATIONS

Sections revealed that destruction of serosa, with one exception, was relatively slight after 45° pads. These adhesions, therefore, tended to become stretched out into thin bands. After 50° or more the small intestine was extensively denuded of serosa and the subserosal tissues became attached to other raw areas or to omentum. An intense fibroblastic response took place in these adherent loops of bowel, which extended in some cases deep into the muscularis. Fibrous replacement began in about two weeks with little or no tendency for the adhesions to become stretched out. When an interposed process of omentum limited the area of attachment between loops of bowel, the bridging of the denuded surfaces by fibrous tissue seemed less marked.

Supravital studies on freshly excised omentum and mesentery stretched over a cork ring showed that an exposure of two minutes at 50° killed some and 55° killed most of the mesothelial cells lining the serosa. This immediate damage to the cells occurred whether the thermal injury was applied by means of hot pads before excision or by immersion in Locke solution after excision.

PERCEPTION OF TEMPERATURE

During operation the surgeon is handicapped in perceiving the approximate temperature of moist laparotomy pads because of the insulating effect of rubber gloves. A pad at 45° C. does not feel warm at all, unless compressed in the cupped hands for some time. A pad at 50° feels comfortably warm after being held for about fifteen seconds. A pad at 55° is noted to be hot after five seconds but can be held indefinitely without discomfort. Only above 55° are painful sensations produced. The perception of heat is more rapid and more accurate when the gloved hand is immersed in the water, since the area of contact is greater and there is no cooling of the water during the period of observation. With immersion 50° is felt as warm in five seconds, while 55° is perceived as hot in three seconds and becomes somewhat uncomfortable in about fifteen seconds. Therefore either method of testing the temperature with the gloved hand is not accurate enough to avoid the use of pads that may cause thermal injury to the serosa. A pad that feels hot to the surgeon is too hot for the delicate peritoneum by some 5 or 10° C.

DISCUSSION

Since hot moist laparotomy pads under the conditions of these experiments caused severe damage to the peritoneum, the question should be raised whether they are necessary for routine packing and retraction. No studies were found in the literature to support the widely held belief that pads below body temperature are harmful. It seems quite unlikely that moist pads at room temperature cause any local damage to the bowel. It is also questionable that their lower temperature would incite reflex changes or cause enough loss of heat to contribute appreciably to the production of shock. It has been adequately demonstrated that refrigerated blood and saline solution at room temperature can be injected intravenously without harm provided the rate of injection is not excessively rapid. In any case temperatures above 45° C. are not necessary to avoid chilling, if the pads are not allowed to become cold before being applied.

Even when warm pads are required in special circumstances, precautions may be observed. In the application of a warm pack to hasten return of circulation in determining the viability of a loop of intestine after release of a strangulation excessive heat would seem particularly

undesirable, since slowing of circulation increases the susceptibility of tissues to thermal injury. Hot packs are frequently employed for hemostasis in the pelvis, gall bladder region, and splenic bed. If contact of such hot packs with the jejunum and ileum is avoided, the likelihood of troublesome adhesions is minimized. The temperature that will most effectively control capillary oozing is above the threshold of thermal injury to the serosa.

SUMMARY

In a series of dogs hot moist laparotomy pads caused injury to the peritoneum and postoperative adhesions. Temperatures of 50° C. (122° F.) for two minutes caused severe damage to the serosa of the small intestine. Some evidence of thermal injury occurred at 45° C.

It is concluded that hot laparotomy pads, except for hemostasis, are unnecessary, harmful, and may play a role in the formation of postoperative peritoneal adhesions in man.

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THE LATE RESULTS IN ACUTE PERFORATED PEPTIC ULCER TREATED BY SIMPLE SUTURE

With Particular Reference to Multiple Ulcer

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ACUTE perforated peptic ulcer still constitutes a grave surgical disease, as regards both early and late prognosis. Since advocacy by Mikulicz[1] in 1880 of simple suture, this in general has been the method of treatment most widely used throughout the civilized world.

The first accurate authentic description of an acute perforated ulcer of the duodenum was apparently made by Penada[2] in 1793. Gerard[3] in 1804 cited a case of spontaneous perforation of the duodenum. Thereafter in the first half of the nineteenth century, there are many references to spontaneous perforations of the intestine, in particular of duodenal ulcers. On reading one of them (Bainbridge[4]) one gathers that the condition was well recognized by leading practitioners of the time, and especially by pathologists.

It was not, however, until after the performance by Billroth in 1881 of the first successful partial gastrectomy, and by Wolfer in 1881 of the first gastroenterostomy, that early operations for acute "perforative peritonitis" were first performed. In the earlier cases, all the patients died, and at autopsy there were found perforated peptic ulcers which frequently had been overlooked at operation. Either Huesner[5] or Kriege[5] in 1892 was the first to suture successfully a perforated gastric ulcer, but the original article does not state which of these two actually performed the operation. And Dean[6] in 1894 was probably the first to suture successfully a perforated duodenal ulcer (though the patient died on the nineteenth postoperative day of intestinal obstruction).

The early history of operations for perforated duodenal ulcers up to 1901 is well recorded by Moynihan,[7] who reported 51 cases, including 2 of his own. In a later article on gastric and duodenal ulcers, Moynihan,[8] as in his article on duodenal ulcers alone, again advocated complementary gastroenterostomy in addition to simple suture, if it appeared "that a stricture of the bowel will inevitably result."

While simple suture has been the most widely used method of therapy, others have also been used; namely, simple suture plus gastroenterostomy, excision of the ulcer combined with some type of pyloroplasty, and primary gastric resection. On a review of the literature, there seems still to exist considerable difference of opinion not only as to the

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

method of choice, but also as to the beneficial results to be obtained from any given method.

The purpose of this article is to report a study of the late results of the treatment of acute perforated peptic ulcer by simple suture; to review the literature on the late results of its treatment by this and other methods; and to point out the frequent high incidence of multiple peptic ulcer.

MATERIAL

From 1921 through 1938 there were admitted to the Roper Hospital 52 cases of acute perforated peptic ulcer treated by immediate operation. Of these cases, 25 survived, while 27 died, a mortality rate of 52 per cent. Of the 25 patients who survived, we have been able to obtain satisfactory follow-up studies in 18.

The 18 cases (see Table I) followed were operated upon by a number of different surgeons. In all of the 18 cases, the treatment was immediate operation with simple suture. However it is to be noted that in 5 of the 18 cases, other procedures in addition to simple suture were performed. In Case 3, the ulcer was "cauterized" preliminary to simple suture. In Case 5, the ulcer was "cauterized with the actual cautery" preliminary to simple suture at the primary operation. In Case 6, the ulcer was "cauterized with the actual cautery" and associated appendectomy was also performed. In Case 7, the ulcer was "cauterized with iodine" preliminary to simple suture. In Case 10, the ulcer was "cauterized and excised with the actual cautery" preliminary to simple suture.

In this series, there were no cases treated by excision of the ulcer plus pyloroplasty, by simple suture plus gastroenterostomy, or by primary partial gastrectomy.

The purpose of the data, gathered on these 18 patients, was to determine the late results of the primary operation. In each case, the patients were personally interviewed and examined by the author, except those cases who had had readmission to the hospital subsequent to the primary operation, and were found "not well" at that time. All cases classified as "well" had recent examination. In no case was a questionnaire resorted to. The late results of any secondary operations performed on any of the patients were not determined.

The late result of the primary operation in each case is classified either as "well" or "not well." In reviewing the literature, the classification of the late results as given by other authors is anything but uniform. In this series, by the term "well," it is meant that the patient considered himself well, able to work with freedom from pain and vomiting, that little or no care had to be taken regarding the diet, and that roentgenologic examination of the stomach and duodenum after a barium meal showed no evidence of an active peptic ulcer. (In one of

the 6 cases classified as "well," a roentgenologic examination could not be obtained.) By the term "not well," it is meant that the patient continued to have, or had at some time subsequent to the primary operation, symptoms which could be attributed to the persistence or recurrence of a peptic ulcer or complications therefrom. In all of the 18 cases, save 2, the presence or absence of a peptic ulcer or complications such as pyloric obstruction was proved at subsequent operation, autopsy, or roentgenologic examination. (In 1 of the 12 cases classified as "not well," the roentgenologic examination was refused, and the diagnosis was made on what was considered indisputable clinical evidence.)

The site of the ulcer at the primary operation was gastric in 4 cases, pyloric in 5 cases, and duodenal in 9 cases. These were the sites as recorded, but in several cases it was stated in the record, as is well known, that the exact localization was difficult to determine due to the presence of a fibrinous exudate on the serosa about the ulcer, obscuring the pyloric vein. In this series, all of the ulcers were on the anterior wall of the stomach, pylorus, or duodenum. In no case were multiple ulcers observed at operation.

Of the 18 cases followed in order to determine the late results of the primary operation, 6 cases, or 33 per cent, were found to be "well" and 12 cases, or 67 per cent, were found "not well," after varying periods of time elapsed following the primary operation. The duration of time since the primary operation for which the cases classed as "well" were followed was 9, 6, 4, 2½ years, and 1 year. In the "not well" cases, the time followed varied from 7 months to 8 years.

Six of the 18 cases, or 33 per cent, were subjected to secondary operation. Three of the 6 cases required immediate secondary operation for a subsequent acute perforation. In these 3 cases, the second perforation occurred from 1 to 5 years following the primary perforation. Thus, 3 of the 18 cases, or 17 per cent, had a second perforation. The other 3 secondary operations were gastroenterostomies. In 1 case, gastroenterostomy was performed for pyloric obstruction two years following the primary operation. In the other 2 cases gastroenterostomy was performed for the persistence of symptoms 1 year, and 2 years following the primary operation.

With full realization of the small number of patients in the series, an attempt was made to determine any possible relationship between patients remaining well or having persistence or recurrence of symptoms, and the following factors: age, race, duration of ulcer symptoms prior to primary operation, duration of primary perforation prior to closure, the site of the ulcer, the size of the ulcer, the use of drainage at the primary operation, complications of the primary operation, and the diet and occupation after the primary operation.

In the cases followed, the ages of the 6 patients who remained well following the primary operation varied from 23 to 48 years, while the

TABLE I

SUMMARY OF PATIENTS WITH ACUTE PERFORATED PEPTIC ULCER TREATED BY SIMPLE SUTURE

CASE NO.	UNIT NO.	AGE	SEX	RACE	DURATION ULCER SYMPTOMS PRIOR TO PERFORATION	DURATION OF PERFORATION PRIOR TO CLOSURE	DATE OF OPERATION	SITE OF ULCER	SECONDARY OPERATION	DATE OF LAST FOLLOW-UP	SYMPTOMS	GASTROINTESTINAL SERIES	REMARKS	TIME FOLLOWED	LATE RESULT OF PRIMARY OPERATION
1	15591	26	M	W	2 yr.	26 hr.	3/11/29	Duodenal	Simple suture of perforated duodenal ulcer 12/14/34	December, 1934	Recurrent acute perforation		Recovery but no follow-up since secondary operation for reperforation	5 yr.	Not well
2	59744	38	M	C	2 yr.	15 hr.	12/18/30	Pyloric	Gastroenterostomy 7/ 5/32	July, 1932	Symptoms and signs of pyloric obstruction		Died 1939 of cerebral hemorrhage; history since second operation not known; no autopsy	2 yr.	Not well
3	62090	36	M	W	10 yr.	6 hr.	11/18/31	Duodenal	No	June, 1940	"Gas on stomach" after drinking beer excessively	No evidence of active ulcer	Ulcer "cauterized" at time of closure	9 yr.	Well
4	67095	18	M	W	4 yr.	18 hr.	7/20/32	Pyloric	No	July, 1940	Abdominal pains before and after meals	Active pyloric ulcer	Patient says he has been unable to work because of stomach trouble	8 yr.	Not well
5	65813	53	M	W	8-9 yr.	3 hr.	4/ 8/32	Gastric	Gastroenterostomy 11/28/33	November, 1933	Abdominal pain and melena	Deformed pylorus and duodenum	Ulcer cauterized with "actual cautery" at primary operation; "old ulcer" healed at second operation; died 1935 of malaria; no autopsy	18 mo.	Not well

6	68908	24	M	W	1 yr.	7 hr.	11/30/32	Duodenal	Gastroenterostomy 1/30/34	June, 1940	None since secondary operation	Normally functioning gastroenterostomy	Ulcer cauterized with "actual cautery" and associated appendectomy at primary operation; secondary operation for persistence of symptoms and not pyloric obstruction	8 yr.	Not well
7	78713	41	M	W	3 wk.	6½ hr.	11/ 9/34	Duodenal	No	May, 1940	Occasional gas; no pain	No evidence of active ulcer	Ulcer cauterized with iodine; patient has considered himself well	6 yr.	Well
8	81301	51	M	C	3 yr.	7 hr.	5/ 4/35	Pyloric	Simple suture perforated gastric ulcer 5/23/36	January, 1938	Persistent ulcer symptoms	Active duodenal ulcer	At secondary operation site of previous perforation not located	3 yr.	Not well
9	84314	25	M	C	2½ mo.	11 hr.	12/10/35	Pyloric	No	July, 1940	Severe pain and hematemesis	Refused	Intermittent symptoms since perforation; reoperation refused	5 yr.	Not well
10	89118	48	M	W	"Long time"		10/13/36	Gastric	No	May, 1940	No symptoms	No evidence of active ulcer	Ulcer cauterized and excised with "actual cautery" at primary operation	4 yr.	Well
11	92125	47	M	C	11 yr.	6 hr.	4/ 8/37	Duodenal	Simple suture perforated duodenal ulcer 8/9/39	August, 1939	Recurrent acute perforation		Recovery from secondary operation; died October, 1939, of unrelated empyema; autopsy: multiple duodenal ulcers	2 yr.	Not well

TABLE I—Cont'd

CASE NO.	UNIT NO.	AGE	SEX	RACE	DURATION ULCER SYMPTOMS PRIOR TO PERFORATION	DURATION OF PERFORATION PRIOR TO CLOSURE	DATE OF OPERATION	SITE OF ULCER	SECONDARY OPERATION	DATE OF LAST FOLLOW-UP	SYMPTOMS	GASTROINTESTINAL SERIES	REMARKS	TIME FOLLOWED	LATE RESULT OF PRIMARY OPERATION
12	92777	23	M	W	3 wk.	8 hr.	5/18/37	Duodenal	No	December, 1937	Recurrence of symptoms	Active duodenal ulcer		7 mo.	Not well
13	97462	37	M	W	2 yr.	9 hr.	3/19/38	Gastric	No	August, 1940	Occasional "gas and heartburn" but nothing like preoperative symptoms	No evidence of active ulcer		2½ yr.	Well
14	98782	52	M	C	2 yr.	7 hr.	6/16/38	Gastric	No	June, 1940	Recurrence of symptoms and tarry stools	Active duodenal ulcer	Well until 1 mo. ago	2 yr.	Not well
15	101410	23	M	W	4-6 wk.	3 hr.	11/30/38	Pyloric	No	May, 1940	None	Healed duodenal ulcer		18 mo.	Well
16	101741	42	M	W	8 yr.	10 hr.	12/30/38	Duodenal	No	June, 1940	Cannot eat anything because of pain	Active duodenal ulcer		17 mo.	Not well
17	104473	43	M	C	6 yr.	5 hr.	6/ 7/39	Duodenal	No	July, 1940	None			1 yr.	Well
18	104762	29	M	C	None	9 hr.	6/25/39	Duodenal	No	May, 1940	Epigastric pain for past month	Active duodenal ulcer		1 yr.	Not well

ages of the 12 patients who did not remain well following the primary operation varied from 18 to 53 years. Thus it did not appear that age was a factor in the late result.

All of the 18 patients followed were males.

Seven of the 18 patients followed were negro. Of these 7, only 1 remained well. The other 11 patients followed were white, and of these 5 remained well while 6 did not.

In the 6 patients who remained well, the duration of ulcer symptoms prior to perforation varied from 3 weeks to 10 years. In the 12 who did not remain well, the duration of ulcer symptoms varied from 3 weeks to 11 years, and 1 of these 12 patients who did not remain well gave no history of ulcer symptoms whatever prior to perforation. Thus it did not appear that the duration of ulcer symptoms prior to perforation was a factor in the late result.

In 5 of the 6 patients remaining well in whom the duration of perforation prior to primary closure was known, the duration varied from 3 to 9 hours, with an average of 6 hours. In the 12 patients not remaining well, the duration varied from 3 to 26 hours, averaging 10 hours. This difference did not appear to be a significant factor in the late result.

The site of the ulcer at the primary operation did not appear to be a factor in the late result. In Table II is shown the site of the ulcer in those remaining well and in those not remaining so.

TABLE II

SITE OF ULCER IN RELATION TO LATE RESULT

	CASES WELL	CASES NOT WELL
Gastric	2	2
Pyloric	1	4
Duodenal	3	6

In 9 of the 18 cases in which it was stated, the size of the ulcer at the primary operation varied from 1 to 3 cm. in diameter, and did not appear to be a factor in the late result.

Drainage at the primary operation was instituted in all but 5 of the 18 cases, and did not appear to be a factor in the late result.

Complications of the primary operation occurred in 8 of the 18 cases. In 5 of the 8 cases, infection of the wound occurred; in another, disruption of the wound; in another, a pelvic abscess; and in the other a subdiaphragmatic abscess followed by a peritoneopleurobronchial fistula. Of the 8 cases complicated, only 1 remained well—the 1 complicated by a pelvic abscess. In the 10 cases uncomplicated, 5 remained well and 5 did not. Even so, complications of the primary operation did not appear to be a factor in the late result.

In 11 of the 18 cases in which it was recorded or ascertained, 7 patients followed a diet and 4 followed no diet after the discharge from

the hospital following the primary operation. The diets followed were of the "soft, bland" variety, and were followed in no case less than two months, and in several cases for as long as a year. Of the 7 patients following a diet, 2 remained well and 5 did not remain so. Of the 4 following no diet, 2 remained well and 2 did not remain so. Thus it would appear that the diet of the variety stated above following the primary operation was not a significant factor in the late result.

The occupation following the primary operation was known in 10 of the 18 cases. Four of the 10 patients remained well; 3 of the 4 did very heavy work, such as stevedoring, while the other was a salesman. Six of the 10 patients did not remain well; 4 of the 6 did heavy work, 1 was a clerk, and 1 was unable to work because of abdominal pain. Thus the occupation following the primary operation was not a factor in the late result.

Six of the 18 patients followed, and therefore 6 (50 per cent) of the 12 patients not remaining well after the primary operation, had secondary operations. Three of the 6 secondary operations were emergency operations for a second perforation. Two of the 3 cases of reperforation were duodenal ulcers at both the primary and secondary operations, while the third was a perforated pyloric ulcer at the primary operation and a perforated gastric ulcer at the secondary operation. The other 3 patients having secondary operation all had gastroenterostomies performed. In 1 case, the gastroenterostomy was performed for pyloric obstruction, while in the other 2, it was performed for persistence of ulcer symptoms. In the 3 patients having gastroenterostomy, the site of the ulcer at the time of the primary operation was 1 gastric, 1 pyloric, and 1 duodenal, in each instance. Thus it would appear that there were no factors of significance relating to the late result as regards secondary operations.

REVIEW OF LITERATURE

There have been many reports by various authors of the late results in the treatment of acute perforated peptic ulcer by the different methods which have been used.

The four methods which have been used are simple suture, simple suture with complementary gastroenterostomy, excision of the ulcer with complementary pyloroplasty, and primary gastric resection. The number of reports on the late results by the different methods have appeared in relative frequency in the order named above, as one would expect.

In the various reports, the systems of classification vary considerably. Thus one finds the results classified according to Grades I, II, III, IV. In another, one finds three groups: free of complaint; having symptoms but able to carry on their work on a strict diet; and required reoperation. In another, the cases are reported as: cured; having grave

troubles; and having dyspepsia. Various further examples of the lack of uniformity in classification of the reported late results could be given at length.

Suffice it to say that for the purpose of making comparable the reports in the literature and the report of this series, all of the previously reported late results have been reclassified by the author, into two groups, "well" and "not well." For instance, in the case of one of the examples cited above, those classified as cured are reclassified in this article as "well," and those classified as having grave troubles and having dyspepsia are reclassified in this article in the single group of "not well." In other words, those reclassified as "well" in this article are the patients reported as those considering themselves well, free of stomach trouble, able to carry on their usual work with freedom from pain and vomiting, and having to exercise little or no care regarding their diet. All others are reclassified as "not well."

Only those previous reports are cited in the foregoing tables in which there are definitely stated in the original article by the author, the site of the ulcer at the primary operation, the type of operation performed in each case, the time followed after operation, and in which it was considered satisfactory criteria for study of late results were used, in particular reference to the exclusion of those series in which the

TABLE III

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCER TREATED BY SIMPLE SUTURE

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL	NO. OF ALL FOLLOWED CASES HAVING REOPERATION
Brown[9]	1925	26	16 (60%)	10 (40%)	
Mills[10]	1925	7	1 (14%)	6 (86%)	1 (14%)
Platou[11]	1929	25	6 (24%)	19 (76%)	11 (44%)
Urrutia[12]	1929	22	11 (50%)	11 (50%)	5 (23%)
Dineen[13]	1929	95	77 (81%)	18 (19%)	10 (11%)
Bryce[14]	1930	100	32 (32%)	68 (68%)	15 (15%)
Hinton[15]	1931	43	23 (53%)	20 (47%)	8 (18%)
White and Patterson[16]	1931	19*	13 (68%)	6 (32%)	2 (10%)
Shelley[17]	1932	29	15 (51%)	14 (49%)	
Gilmore and Saint[18]	1932	44	17 (40%)	27 (60%)	
Scotson[19]	1933	63*	25 (40%)	38 (60%)	
Rousselins[20]	1933	27	12 (44%)	15 (56%)	5 (19%)
Calvet[21]	1935	15	5 (33%)	10 (67%)	5 (33%)
Sallick[22]	1936	45	16 (36%)	29 (64%)	
Guthrie and Sharer[23]	1936	53*	41 (77%)	12 (23%)	10 (19%)
Cabiglio[24]	1936	37	20 (54%)	17 (46%)	7 (19%)
Mariné[25]	1936	10	3 (30%)	7 (70%)	
Raven[26]	1936	58*	32 (55%)	26 (45%)	13 (23%)
Cable[27]	1938	24	8 (33%)	16 (67%)	
Eliason and Thigpen[28]	1938	22	15 (70%)	7 (30%)	4 (18%)

*All duodenal ulcers.

results of questionnaires were used, without personal interviews and examinations of the patients.

In Table III are shown the previously reported late results of the treatment of acute perforated peptic ulcer by simple suture. It is to be noted that the percentage of cases followed remaining well, varied from a high of 86 per cent to a low of 14 per cent. And conversely, of course, the percentage not remaining well varies from a low of 14 per cent to a high of 86 per cent. As an average, of the total number of 764 cases followed, 388, or 51 per cent, remained well, while 376, or 49 per cent, did not remain well. In the reports in which it was recorded, of a total number of 524 cases followed, 96, or 18 per cent, were subjected to secondary operation.

TABLE IV

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCER TREATED BY SUTURE PLUS GASTROENTEROSTOMY

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL
Mills[10]	1925	14	10 (70%)	4 (30%)
Dineen[13]	1929	7	5 (71%)	2 (29%)
Platou[11]	1929	15	15 (100%)	0
Urrutia[12]	1929	12	4 (33%)	8 (67%)
Judine[29]	1929	48	25 (52%)	23 (48%)
White and Patterson[16]	1931	6	4 (67%)	2 (33%)
Shelley[17]	1932	19	16 (84%)	3 (16%)
DeMourges[30]	1932	68	42 (62%)	26 (38%)
Scotson[19]	1933	14	8 (57%)	6 (43%)
Rousselins[20]	1933	3	3 (100%)	0
Mariné[25]	1936	30	19 (63%)	11 (27%)
Raven[26]	1936	59	39 (68%)	20 (32%)
Curtillet[31]	1937	12	8 (67%)	4 (33%)
Eliason and Thigpen[28]	1938	21	16 (76%)	5 (24%)

In Table IV are shown the previously reported late results of the treatment by suture plus gastroenterostomy. Here, again there is considerable variation in the number of patients remaining well, varying from a high of 100 per cent to a low of 33 per cent. Of the total number of 328 cases followed, 214, or 65 per cent, remained well, while 114, or 35 per cent, did not remain well.

TABLE V

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCERS TREATED BY EXCISION PLUS PYLOROPLASTY

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL
Rowlands and Turner[32]	1927	12	7	5
Grimault[33]	1929	10	10	0
Williams and Walsh[34]	1930	6	5	1
Hinton[15]	1931	5	1	4

In Table V are shown the previously reported late results of the treatment by excision and pyloroplasty, of which there have been comparatively few. Thus, of a total of 33 cases followed, 23, or 70 per cent, remained well, while 10, or 30 per cent, did not remain well.

TABLE VI

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCERS TREATED BY PARTIAL GASTRECTOMY

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL
Paul[35]	1922	11	11	0
Hromada and Newman[36]	1922	13	13	0
Odelberg[37]	1927	8	7	1
Luquet[38]	1936	2	2	0
Mariné[25]	1936	19	19	0

In Table VI are the previously reported late results of the treatment by primary partial gastrectomy, of which there have also been comparatively few. Of a total of 53 cases followed, 52, or 98 per cent, remained well, while only 1 case, or 2 per cent, did not remain well.

DISCUSSION

From a study of the literature and of the series herein reported it is apparent that the late results of the treatment of acute perforated peptic ulcer are poor, except by primary gastric resection. That is, in those treated by simple suture, it is safe to say that approximately 50 per cent will not remain well, and an appreciable number of these will necessarily have to have some subsequent operation. The late results of the treatment by suture plus gastroenterostomy and by excision plus pyloroplasty as reported are more favorable, but the reasons for this are certainly not clear.

There should be a definite reason for these poor results, and the most likely reason would seem to be the existence of multiple peptic ulcers in an appreciable percentage of the patients presenting the disease of peptic ulcer.

In the series herein reported, some of the patients remained apparently perfectly well until a year or two following the primary operation, only then to have a recurrence of symptoms. Other authors[24] have reported cases in whom the symptoms have recurred as long as five years after the primary operation. In such cases, it seems only logical either that an old ulcer has become active again or that one or more new ulcers have appeared. In this series, one of the patients having two perforations had a pyloric ulcer at the primary operation and a gastric at the secondary. Not included in this series because of death by generalized peritonitis is a recent patient upon whom I operated for perforated duodenal ulcer. At autopsy, there was a duodenal ulcer on the posterior wall, immediately opposite a perforated ulcer on the anterior wall. It is perfectly obvious that this patient would probably have had persistent symptoms even if the anterior wall ulcer healed completely and promptly.

A significant incidence of multiple ulcers, or scars considered to be the result of previous peptic ulceration, is further borne out by a study of pathologic material.

In the surgical pathologic protocols in the Department of Pathology, we find in 9 stomach specimens resected for peptic ulcer that in 3 of the specimens there were multiple ulcers and/or scars; in one of the 3 specimens there were five ulcers and an old scar; in another there were an old ulcer and an old scar; in the third there were "multiple" ulcers. In an additional 5 specimens consisting of the pyloric end of the stomach and the first portion of the duodenum, the ulcers were solitary. In an additional duodenum specimen, there were two ulcers. Thus, in a total of 15 specimens observed, multiple ulcers and/or scars occurred in 4 cases (27 per cent).

In a study of the autopsy protocols in the Department of Pathology, peptic ulcer was encountered in 44 cases. These cases consisted of all those patients in whom some complication of an ulcer was the cause of death, and also those in whom peptic ulcer was an incidental finding.

In 27 autopsy cases presenting gastric ulcer alone, multiple ulcers and/or scars occurred in 7. These 7 cases consisted of 1 case of "multiple" ulcers; 3 cases of two ulcers; 1 case of an ulcer and a scar; 1 case of two ulcers of which one was perforated; and 1 case of five ulcers of which one was perforated.

In 3 autopsy cases, combined gastric and duodenal ulcers and/or scars were found. In 1 case there was an ulcer in both the stomach and duodenum; in another an ulcer in the stomach and a scar in the duodenum; and in the third case there were two ulcers in the stomach, one of which was perforated, and a scar in the duodenum.

In 1 autopsy case, there were two gastric ulcers, one pyloric ulcer, and one duodenal ulcer.

In 1 autopsy case, there was a single pyloric ulcer.

In 12 autopsy cases presenting duodenal ulcer alone, multiple ulcers and/or scars were present in 5 cases. These 5 cases consisted of 2 cases of an ulcer and a scar; 1 case of "multiple" ulcers of which one was perforated; and 2 cases of an ulcer on both the anterior and the posterior walls, the anterior wall ulcer being perforated in each case.

Thus, in a total of 44 autopsy cases presenting peptic ulcer, there were multiple ulcers and/or scars in 16 cases, or 36 per cent.

In the 44 autopsy cases, perforation of an ulcer had occurred in 11 cases. In these 11 cases, the incidence of multiple ulcers and/or scars was even higher, being 55 per cent (6 of 11 cases).

And, considering the combined autopsy and surgical pathologic material, in a total of 59 cases, multiple ulcers and/or scars occurred in 20, or an incidence of 34 per cent.

The frequent existence of multiple peptic ulcer is by no means unknown. Dunbar[39] stated that "when perforation had occurred at the duodenum, and when a post mortem was obtained, a large proportion showed a second ulcer nearly always opposite the perforation." Luquet[38] remarks on "kissing ulcers." Lewisohn[40] stated that in about 50 per

cent of patients with duodenal ulcer, two or more ulcers were found in specimens after partial gastrectomy.

Graves,[41] in a review of the German literature on peptic ulcer, stated that the high incidence of multiple peptic ulcer was used by German surgeons as their justification for their frequent practice of primary gastrectomy for perforated ulcer. He cites various authors as reporting multiple peptic ulcers in a high percentage of cases varying from 20 to 50 per cent. Among them were Schulein[43] who reported the incidence in 20 per cent, Petren[43] in 27 per cent, and Speck[44] in 50 per cent.

More recently, Guszich[45] has reported 7 cases of multiple ulcer (6.2 per cent) among 113 cases of perforated gastric and duodenal ulcers. He quotes various authors as reporting a much higher incidence. Zuckschwerdt and Eck[46] found in their autopsy material multiple ulcers in 29 per cent of the peptic ulcer cases, and Brunner[47] in his, either multiple ulcers or scars in 43 per cent. Brütt[48] found in his autopsy material 10 cases (53 per cent) of multiple ulcer among 19 cases of duodenal perforation, while in his resection material, the incidence was 17 per cent in the cases of peptic ulcer without perforation, and 70 per cent in the cases of peptic ulcer with perforation. Koennecke[49] reported the incidence of multiple ulcer as 50 per cent in his duodenal ulcer cases.

Granting that the incidence of multiple peptic ulcer in this clinic and others appears very significant, indeed, the wisdom of simple suture of perforated peptic ulcers as a routine method of treatment might be questioned. To be sure, the reported mortality statistics[50] for the other types of operation are often better, and those for primary gastric resection are even best. However, mortality statistics can be very misleading, and one can find almost any mortality rate desired for any given type of operation, depending almost entirely upon the lapse of time between perforation and operation, as is well known.

The late results for the other types over simple suture are reported as better, and again, as one would expect, those for primary gastric resection even best. However, even in view of the various considerations for and against the different types of operation,[16, 50] the primary consideration is still the survival of the patient. For this, one can hardly deny that simple suture is the easiest, quickest, and safest, and affords the patient the best possible chance of immediate recovery at any stage following perforation. To do anything further in the way of a curative procedure in the presence of an acute perforation merely subjects unnecessarily an estimated 50 per cent of patients to additional risk.

The most important consideration, however, as a result of this study, is the fact that these patients should be carefully followed at frequent intervals over a long period of time, possibly five years, in view of the large percentage who do not remain well. In the event of subsequent complete pyloric obstruction without the additional presence of an ulcer,

gastroenterostomy is known to be highly successful. And in the event of a persistence or recurrence of symptoms, in view of the large percentage of patients with multiple ulcer, secondary gastric resection is to be recommended.

SUMMARY

1. The late results in 18 cases of acute perforated peptic ulcer treated by simple suture are reported. Six patients (or 33 per cent) remained well, and 12 patients (67 per cent) did not remain well.

2. Six of the 18 patients were subjected to secondary operation, 3 of these being for a subsequent second perforation.

3. The late result in relation to age, duration of symptoms, diet and other factors, was studied without significant findings.

4. The late results reported in the literature for treatment by simple suture, suture plus gastroenterostomy, excision plus pyloroplasty, and primary gastric resection are reviewed.

5. In this clinic, the incidence of multiple peptic ulcers and/or scars in the surgical pathologic material was found to be 27 per cent (4 of 15 cases).

6. In this clinic, the incidence of multiple peptic ulcers and/or scars in the autopsy material was found to be 36 per cent (16 of 44 cases).

7. It is felt that this high incidence of multiple peptic ulcer is largely responsible for the poor late results obtained in the treatment of acute perforated peptic ulcer by simple suture.

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THE SURGICAL MANAGEMENT OF POSTRADIATION SCARS AND ULCERS

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THE surgical management of the lesions caused by the tissue-destructive rays of both x-ray and radium presents problems which call for a knowledge of and the application of practically all of the principles of plastic surgery. The earliest report of a case of dermatitis due to x-rays is that of Marcuse, published in 1896. Marcuse[1] also reported a case of malignancy in an area of x-ray dermatitis. Since that time there have been a great number of similar reports. Their appearance in the literature suggests not only that these postradiation lesions probably are increasing in frequency, but that the medical profession is more alert to the value of and also to the dangers of radiation therapy. Undoubtedly, radiologists have given increasingly strict attention to the prevention of the development of these unfortunate complications. This is attested to by the repeated admonitions of competent radiologists with regard to the protection of patient and operator at the time of administration of the rays and also by the improvements in equipment and in the methods of treatment which have steadily expanded the field of usefulness of radiation therapy. It is a commentary on these improvements that clinical reports which appeared in the literature in the second and third decades of this century told of a higher percentage of x-ray ulcers occurring in physicians giving the therapy than in patients so treated. Later reports reversed this proportion. Presumably this is due to a recently born intensity of purpose on the part of radiologists in the therapy of malignant lesions. Such an unfortunate aftereffect as the postradiation ulcer may be condoned if produced in the treatment of inoperable malignancy. However, in the treatment of benign lesions or malignant ones within the scope of surgery, it is difficult to acknowledge the value of a method of therapy which carries with it danger of serious complication.

The burden of management of these postradiation ulcers has fallen upon the surgeons. It is planned to list in this presentation the methods of conservative treatment and also to outline the surgical methods which may be applied to the various types of postradiation scars and ulcers. Case reports giving experiences with the surgical removal of postradiation scars and ulcers will be presented.

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

Clinical examination of the scars produced by x-radiation shows them to be characteristically of firm consistency, depressed below the adjacent surface, and demarcated abruptly from it or blending gradually into the areas of normal adjacent skin. Often there is subcutaneous atrophy, evidencing the penetration of the destructive ray with its resultant subcutaneous fibrosis. The scarred area may be uniformly white in color or it may show areas of pallor alternating with areas of brown coloration. There may be clusters of telangiectases, visible as reddened wormlike areas in the background of white scar tissue. Often these scars are adherent to underlying structures such as fascia, muscle and bone. Their surfaces may be smooth or hyperkeratotic. In the latter type epithelial degeneration into carcinomatous malignancy is suggested. These differ, then, from the hypertrophic scars of thermal burns and they do not have the tendency to local recurrence exhibited by the true keloid.

Observation of the ulcers caused by radiation shows them to be punched-out ulcers, the lateral walls of which are made up of thickened, ischemic fibrous tissue. The most central portion of the scarred area, the point of maximal ischemia, is the area in which ulceration is most likely to occur. The floor of the ulcer may be covered with a thick, sticky, elastic, grayish yellow exudate which is easily removed to expose pale, firm granulation tissue or smooth, dense fibrotic tissue. These ulcers usually are very sensitive and may be excruciatingly painful. On microscopy the corium and subcutaneous tissue are seen to be replaced by dense fibrous tissue often invading the subadjacent fascia and muscle. There is thickening of the walls of the blood vessels with endothelial obliteration. Necrosis of underlying bone is commonly observed. The epithelium shows a flattening of the rete cones and in those cases which have undergone malignant change there are whorl formations of epithelial cells characteristic of the squamous-cell carcinoma. Malignant epithelial tumors of the basal-cell type are also observed in these scars, and sarcomas developing in these lesions have been reported in numbers in the literature. It is difficult to explain the development of malignancy in these ulcers. Repeated trauma to these areas undoubtedly is a factor. The fact that many cases of malignancy have developed in areas of the skin originally treated for inflammatory lesions, such as psoriasis, eczema, and tuberculosis, suggests the possible role of cutaneous infection in the development of the malignancy. Deuticke[2] reported sixty-one cases of roentgen sarcoma following treatment of inflammatory lesions. Experimental work on rabbits reported by Burrows and associates[3] lends support to this idea. They stated that 66 per cent of rabbits to which x-ray had been given after the experimental production of an inflammation of the skin developed carcinoma.

Regarding the dermatological treatment of postradiation scars and ulcers, it may be said that a number of widely different methods have been acclaimed. Treatment with ultraviolet light,[4] Finsen-Reyn lamp,[4]

electrodesiccation,[5] radium, sacrification,[5] trichloracetic acid cauterization,[5] Dodd's solution (containing phenol),[5] ointment containing pancreatic ferments,[6] and the application of fresh leaves of the plant aloe vera[7] have been recommended. The last mentioned has been endorsed by MacKee[8] for ulcers with the qualifying statement that the treatment is of no value in the attempted removal of telangiectases, scars, keratoses, or atrophy. It is generally agreed that the application to the skin of such chemicals as sulfur, scarlet R, mercury, pyrogallic acid, iodine, resorcin, tar, salicylic acid, and cantharides may raise the sensitivity of the skin to the x-ray. It seems likely also that electrodesiccation, actinic ray and radium may act to accelerate further the destruction of tissue rather than to retard it. Essentially, then, the problem presents itself as one of wound healing to be accomplished in tissues known to be deprived of their normal capacity for growth and repair. The additional problem of reconstruction of the surface contour of the affected area demands that all of these lesions be treated by surgical methods.

The methods available in the surgical management of postradiation scars may be listed as follows:

1. Simple excision
2. Excision and primary suture by means of sliding flaps
3. Gradual partial excision
4. Excision and replacement by
    a. Thick-split graft
    b. Whole thickness graft
    c. Pedunculated flap

In the management of the indolent ulcers resulting from radiation therapy the following methods may be utilized:

1. Simple excision
2. Excision and primary suture by means of sliding flaps
3. Excision and replacement by
    a. Multiple small deep grafts after a period of antisepsis to allow granulation tissue to form
    b. Thick-split grafts
    c. Pedunculated flap
4. Amputation
5. Section of regional nerves
6. Periarterial sympathectomy

The type of pedunculated flap to be used depends upon the surface location of the lesion. Thus, gauntlet flaps have been used for the fingers, double pedicled flaps in the region of the anus, tubed pedicles for lesions of the torso, face, neck, and extremity. Amputation is seldom indicated except in those ulcers of the fingers in which the pain is unbearable, or which have become malignant. Periarterial sympathectomy

has been advocated for relief of pain and for its benefit in bringing about healing of the ulcer. Leriche and Fontaine[9] have reported complete cure by this method in 12 of 27 cases, relief from pain and improvement in 7 cases, and failure in 8 cases. Tempsky[10] reported 2 cases in which there was temporary relief from pain and partial healing of the ulcer following periarterial sympathectomy with later recurrence of the painful ulcer. Eddowes[11] in 1910 reported relief of pain and healing following section of regional nerves. Later surgical reports do not emphasize this method of treatment.

The following case reports give the details of surgical treatment in ten cases with which I have had experience at the New York Hospital. The problems presented by these cases comprise many of the problems of indolent wound healing and exhibit nearly all of the methods of surgical treatment.

The first case is one in which x-ray therapy was given for the treatment of an enlargement of the thyroid. The deforming scar later necessitated surgery. The scar was excised and the wound closed by means of sliding flaps. Undoubtedly, surgical treatment of the goiter would have been preferable to x-ray therapy in this case.

CASE 1.—(M. E., N. Y. H. Case 230039.) This is the report of a 33-year-old white woman who noticed a swelling in the left side of her neck for the first time in 1932. A physician told her that this was a goiter and advised x-ray therapy. There were no symptoms of hyperthyroidism. Following intensive therapy over a period of three months in 1933, the swelling completely disappeared. Accurate information concerning the total dosage of x-radiation is not available. Upon completion of the treatment, an ulceration of the skin appeared over the area treated. Dressings were necessary for three months. The resultant deformity was a cause of concern to the patient not only because of its unsightly appearance but also because of the symptom of itching.

Examination, six years after this treatment, showed an ivory white rectangular scar with numerous telangiectases on its surface. It occupied a rectangular area measuring 9.5 by 4 cm. in the left anterior cervical region. The thyroid gland was palpable, the left lobe being slightly larger and firmer than the right. The scar was movable on the underlying tissues but caused visible adherent depression on deglutition. At operation nine months ago the operator was prepared to do a whole-thickness graft, but found that because of the ease with which the flaps of skin and platysma muscle were mobilized in the neck, the wound could be closed by primary suture. Flaps from either side were brought toward the center, the final line of suture conforming to the outline of the letter H. Because the sheath of the platysma could be sutured firmly with buried sutures of fine silk, the tension on the line of suture was not great. Microscopic examination of the tissue removed at operation showed atrophy of the epidermis and replacement of the dermis with dense, avascular, connective tissue. Figs. 1, 2, and 3 show the preoperative appearance, technique of operation, and final result. Follow-up examination nine months after operation showed no recurrence of the condition.

The second case is one in which radium and x-ray therapy, given in treatment of a benign lesion (hemangioma), caused a deforming scar of

the cheek which necessitated three operative procedures to effect its removal by gradual partial excision. Most probably surgical excision of the primary lesion would have been preferable.

CASE 2.—(L. L., N. Y. H. Case 158604.) This is the case report of a 17-year-old girl who was examined for the first time in this clinic in April, 1937. She complained of a rectangular white, depressed scar of the left malar region which resulted from treatment of an angioma during infancy. The mother has described this as a port-wine stain. When she was 15 months old, the region was treated with carbon-dioxide snow to the point of blistering, but without eradication of the lesion. At 18 months of age treatment was instituted with radium plaques and followed by x-ray therapy. In the years before she came to this clinic she consulted dermatologists on several occasions and had been discouraged repeatedly as to the benefit of any further treatment.

Fig. 1. Fig. 2.

Fig. 1.—Case 1. Adherent scar of neck following x-ray therapy for disease of the thyroid gland. Note the central pallor and the telangiectases at the periphery.

Fig. 2.—Case 1. Appearance of the patient two months after excision of the post-radiation scar.

Examination showed a depressed, white, flat scar measuring 3 cm. across and 3.5 cm. from above downward. This was removed by gradual partial excision, three operations being performed in April, 1937, May, 1937, and August, 1938, respectively. All of these operations were done under local anesthesia without hospitalization. The prolonged interval between the second and third stages was occasioned by the fact that minor infection developed in the wound after the second stage. Following each procedure a crepe lisse[12] dressing was employed for six weeks. This consisted of ordinary indestructible chiffon impregnated with collodion and applied over the entire cheek. Such a dressing serves to immobilize the face so that not even facial expression causes movement of the tissues. This relieves the recent wound of undue tension during the early postoperative weeks when ordinary facial mo-

tions may cause undue widening of the scar. Microscopic examination of the tissue removed showed dense reaction of fibrous tissue in the corium and subcutaneous tissue and flattening out of the rete cones of the epidermis. Figs. 4, 5, and 6 show the preoperative appearance, the technique of operation, and the final result. Follow-up examination two and one-half years after the final operation showed no widening of the scar.

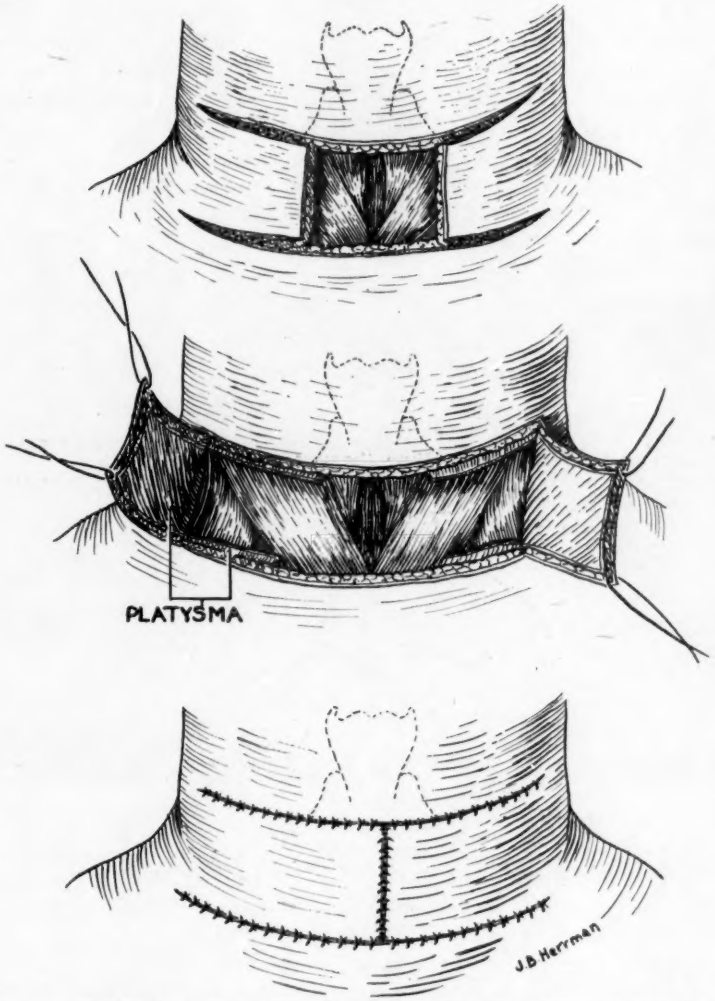

Fig. 3.—Case 1. Technique of excision of scar and plastic closure of defect by means of sliding flaps and primary suture.

The next case is another instance in which x-ray and radium therapy produced a scar which itself constituted as much of a deformity as did the original lesion. In addition the lesion (pigmented mole) was not removed completely, and the treatment caused atrophy of the subcutaneous tissue. Since the patient was subjected to successful surgical excision and surfacing of the defect on the face with a whole-thickness graft, it seems likely that it would have been better to have employed this method of treatment instead of radiation many years earlier.

Fig. 4. Fig. 5.

Fig. 4.—Case 2. Depressed scar of cheek following treatment of an angioma with carbon-dioxide snow, x-ray and radium therapy.

Fig. 5.—Case 2. Result following gradual partial excision of the scar (three-stage operative procedure).

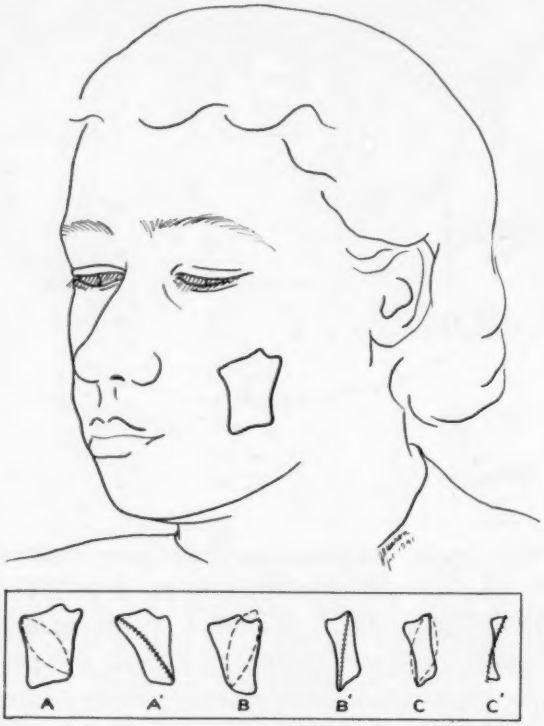

Fig. 6.—Case 2. Diagrammatic sketch showing the steps in excision of a post-radiation scar of the cheek by the method of gradual partial excision. The outline of the extent of excision and suture employed in the first operation is shown in *A* and *A'*; for the second operation in *B* and *B'*; in the third operation in *C* and *C'*.

CASE 3.—(G. W., N. Y. H. Case 250979.) This is the case report of a young woman, 23 years of age, who was treated during infancy for a hairy mole on the right cheek. Acid cauterization was used. Because of the pain caused by this treatment, it was discontinued. At the age of 4 years the patient received prolonged treatments with both x-ray and radium. No accurate information is available as to the total amount of radiation given.

On examination a depressed scar measuring 6.5 by 3.5 cm. was seen over the right malar region. Subcutaneous atrophy was in evidence and the scar itself, while smooth, presented a rather severe deformity, since there were color variations within it from white to red to brown. The brown color apparently was due to residual pigmented nevus since it was limited to a smaller area within the scar, approximately 3 by 4 cm. in size. Evidently the therapy had failed to eradicate completely the hairy mole and also had produced deformity over an area greater than that of the original lesion. There was no regional adenopathy.

Fig. 7. Fig. 8.

Fig. 7.—Case 3. Depressed scar of cheek following treatment of a hairy mole by cauterization, x-ray, and radium. The darker central portion was brown in color due to incomplete removal of the mole.

Fig. 8.—Case 3. Appearance following excision of the pigmented scar and surface replacement by means of a free, whole-thickness graft taken from the abdomen. Photograph taken ten weeks after operation.

On Nov. 14, 1939, under local anesthesia, this scar was excised, care being taken not to damage the fibers of the facial nerve. A whole-thickness free graft of skin was cut from the right lower quadrant of the abdomen according to a tin-foil pattern of the defect on the side of the face. The superficial abdominal defect was closed by excision of subcutaneous fat and undercutting of wound edges. The graft was sutured into place on the face with interrupted sutures of fine black silk. The long ends of these sutures were tied over a gauze pad for immobilization. The incisor teeth were wired together by Dr. Harold Genvert of this clinic. The head dressing, incorporating rubber sponge, was applied over the right cheek and the wound was not inspected until the sixth day after operation, at which time it was seen that the graft had taken in its entirety. The patient was discharged from the hospital on the twelfth day after operation. Microscopic examination of the specimen showed that the corium was replaced by dense fibrous tissue. The rete cones were flattened

out. There was hyperplasia of the nevus cells and beneath the epithelium there were groups of chromatophores containing brown pigment. The preoperative and postoperative photographs are shown in Figs. 7 and 8. Examination fifteen months after operation showed the graft to be smooth, pliable and a good match in color to that of the adjacent skin.

The fourth case is one in which the indication for deep x-ray therapy given in 1918 is not quite clear. Of interest is the fact that a severe skin reaction developed during the course of radiation and healed completely as treatment was continued only to give rise to ulceration eighteen years after the last treatment had been given.

CASE 4.—(M. S., N. Y. H. Case 268989.) This case is that of a 69-year-old American-born housewife who gave the history of having been treated intensively with low voltage x-ray to the lower abdomen twenty-two years earlier. This treatment was given to control hemorrhage following abdominal operation. The history is obscure as to the nature of the operative procedure. Apparently a panhysterectomy had been done, since, at the time of admission to the New York Hospital, examination revealed that none of the pelvic organs could be palpated. During the course of x-ray therapy a severe skin reaction developed over the lower abdominal wall. This healed spontaneously and the patient was free from symptoms until four

Fig. 9.—Case 4. Benign ulcer of the lower abdominal wall which developed in an area of radiodermatitis eighteen years after the last x-ray treatment had been given.

years before admission to this hospital. This was eighteen years after the last x-ray treatment had been given. At that time a thickening of the skin in the right lower quadrant of the abdomen was noticed. This developed into a hard cutaneous mass which crusted and ulcerated alternately. Six months before admission, eczema of the abdominal wall, limited to the two lower quadrants, developed. This responded to therapy with lotions, and on July 23, 1940, the patient was admitted to the New York Hospital for excision of the crusted, elevated lesion of the skin of the right lower abdominal quadrant. The appearance of the lesion at the time of admission to the hospital is shown in Fig. 9. On examination of the abdomen it was seen that there was excessive cornification of the skin of the lower abdominal wall. Just over McBurney's point there was an elevated, hard tumor of the skin 2 by 2 cm. in size. In its central portion there was a small ulcer. This lesion had the appearance of an epithelioma. At operation this area was widely excised through a transverse, elliptical incision. This incision was carried through the fibrotic subcutaneous tissue and the thickened anterior rectus fascia. The wound was closed with mattress sutures without drainage. Microscopic examination of the specimen showed a thickened, hyperkeratotic epidermis overlying a thick layer of scar tissue and fat in

which there were collections of chronic inflammatory cells. There was no evidence of malignancy. Superficial wound infection developed. This was readily controlled. The patient was discharged from the hospital on Aug. 14, 1940, twenty-one days after operation. Two weeks later the wound was entirely healed. On examination six months after operation it was determined that there had been no further symptoms. Photograph of the appearance of the lower abdomen on February 5, 1941, is shown in Fig. 10.

The fifth case is an example of the development of severe skin reaction with resultant chronic ulceration following intensive x-radiation for the treatment of glandular metastases from a malignant melanoepithelioma. It is this type of case in which the radiologist and surgeon justifiably may agree to carry the patient up to the limit of skin tolerance of the x-ray in the attempt to control a disease which is beyond the scope of surgery.

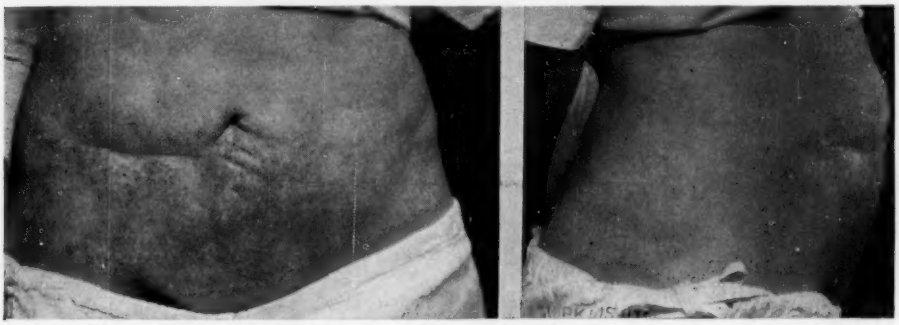

Fig. 10.—Case 4. Appearance of the lower abdomen six months after excision of the benign ulcer due to radiodermatitis.

CASE 5.—(M. S., N. Y. H. Case 261163.) This report is that of a 44-year-old American single, white female, who was examined for the first time on March 14, 1940, because of the complaint of a swelling below the left clavicle. The history revealed that eleven years earlier the left ring finger had been amputated at another institution. Report from that hospital revealed that the lesion of the finger was diagnosed microscopically as a malignant melanoepithelioma. A lymph node was removed from the infraclavicular region. Microscopy showed this to be a metastasis. X-rays of the neck and chest revealed no sign of other metastases. Over a period of six weeks x-ray therapy was given through three portals as follows: left infraclavicular, 4,700 R.; left lateral neck, 4,700 R.; left infraclavicular (lateral), 2,000 R.

X-ray therapy had to be discontinued because of a severe skin reaction over the left cervical and infraclavicular regions. There was a large raw surface covered with a yellow exudate. The infraclavicular swelling had disappeared. There was subsequent softening of tissue in the central part of this wound with the result that as epithelialization occurred over the major part of the wound, this central portion persisted as an ulcer. Dry sterile dressings were applied daily and excision of the ulcer was contemplated, but the patient entered the hospital in a comatose state eight months after the metastasis in the infraclavicular region had been revealed. The patient expired on Dec. 22, 1940. Death was due to hemorrhage into the cerebellum and pons. Microscopic examination of the ulcer of the chest wall showed dense fibrosis, avascular granulation tissue, and replacement of the subcutaneous tissue with fibroblasts. Photograph of the lesion is shown in Fig. 11.

Another case report is one in which the postradiation effect (ulceration of the abdominal wall) is justified in view of the fact that the therapy in this case has effected control of malignant disease.

CASE 6.—(C. S., N. Y. H. Case 78062.) This is the report of a 57-year-old German-born housewife who was given five series of x-ray treatments to her lower abdomen for squamous-cell carcinoma of the cervix in 1934 and 1935. The total amount of x-radiation given was 18,280 R. units; 3,600 mg. hours of radium were applied. The last treatment was given in 1935. The lesion of the cervix healed completely without extension. There had been no evidence of recurrence of carcinoma up to April 11, 1940, so that the patient has been listed as a five-year carcinoma cure.

Fig. 11.—Case 5. Ulcer of anterior chest wall following intensive x-radiation (11,400 R. over a period of six weeks) for metastatic melanoepithelioma.

In December, 1938, the patient was admitted to the hospital because of the late development of ulceration of the lower abdominal wall. This came on three years and three months after the last x-ray treatment was given.

Examination showed a brawny indurated area covering the lower abdomen, with scarring of the skin and numerous telangiectases. Two ulcers measuring 3 and 4 cm. in diameter were present within the scar. These presented an unhealthy gray granulation tissue, from the surface of which *Staphylococcus aureus* was cultured. In January, 1939, this patient was operated upon under general anesthesia. A large elliptical incision with its long axis transverse was made around the scar. Laterally, this incision extended to the iliac crests on both sides, superiorly to a point 3 cm. below the umbilicus, inferiorly to the symphysis pubis. The incision was carried down to the fascia of the external oblique on both sides. The tissue was almost completely avascular. The induration extended into the rectus muscle but not into the peritoneum. Microscopic examination of the tissue removed revealed atrophy of the epidermis, fibrosis of the derma, and subcutaneous scar with acute inflammation. Thrombosis of large vessels in the subcutaneous tissue was noted. Without opening

the peritoneal cavity the operator was able to overlap the fascial structures from above downward with mattress sutures of chromic catgut, after the technique of the Mayo hernioplasty. Postoperatively, there was an elevation of temperature and liquefied fat discharged from the right side of the wound. Culture again showed *Staphylococcus aureus*. All sinuses were healed in March, 1939, two months after the operation. The patient was seen in March, 1940, fourteen months after the

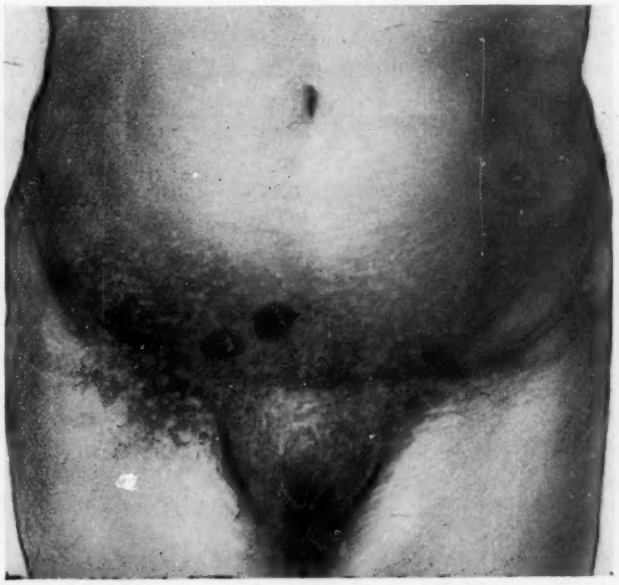

Fig. 12.—Case 6. Lesion of lower abdominal wall with ulceration and extensive regional fibrosis. This followed intensive treatment with x-ray and radium for squamous-cell carcinoma of the cervix.

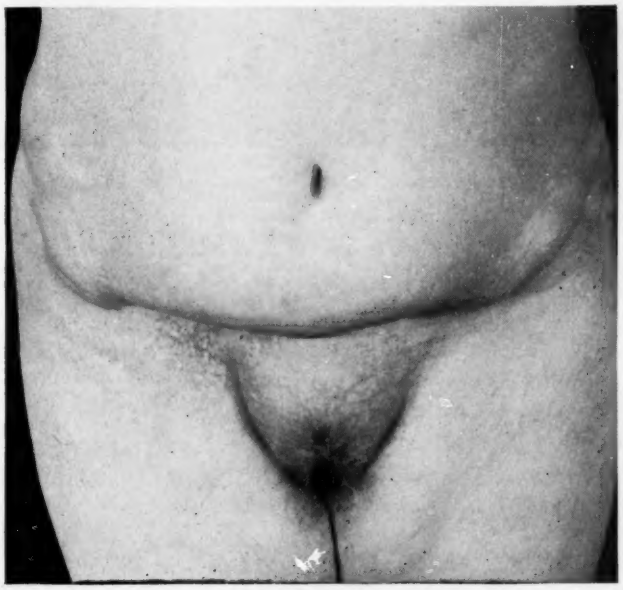

Fig. 13.—Case 6. Appearance of the abdomen seven months after excision of the ulcerated and infected area. This patient was examined five years after the last radiation treatment was given and fifteen months after surgical excision of the lesion of the lower abdominal wall. No recurrence of carcinoma could be demonstrated at that time and the wound of the abdominal wall remained healed.

excision. There was no recurrence of carcinoma at that time and the wound remained healed. Figs. 12 and 13 show the appearance of the lower abdomen before and after operation.

The seventh case is an example of the development of malignant ulcer following x-ray treatment of a chronic inflammatory condition of the skin (psoriasis). The reports of Deuticke,[2] who listed 61 cases of malignancy following x-ray therapy for lupus, psoriasis, eczema, hypertrichiasis, and other inflammatory conditions, and of Witwer and

Fig. 14.—Case 7. Photograph of ulcerated area overlying the right lower fibula. X-ray treatment had been given to this area as well as to other parts of the body three years before the development of the ulcer. In the sixteen months before this photograph was taken this area repeatedly broke open and ulcerated. The skin around the ulcer was fibrotic, dry, hairless, and hyperkeratotic. Rather typical lesions of psoriasis show higher on the leg and over the posterior aspect of the lower leg. Microscopic examination of this lesion showed it to be a squamous-cell carcinoma.

Leucutia,[13] who recorded the development of malignancy in 20 cases after x-ray therapy for acne, keloid, hyperkeratosis, psoriasis, ringworm, sycosis barbae, etc., indicate that the sequence of events which occurred in this sixth case is well known. Unless x-ray therapy affords good probability of cure, it is not justified in the treatment of these chronic inflammatory diseases of the skin.

Case 7.—(C. W., N. Y. H. Case 286661.) This case report is that of a 36-year-old American-born stock broker who had suffered from psoriasis with lesions over his back, elbows, and legs for fourteen years. In June, 1935, x-ray treatments were started. These were given once a week for three weeks; similar treatments were given every two months over a period of eighteen months. In December, 1936, the

last x-ray treatment was given. In September, 1939, the patient injured the outer aspect of the lower third of the right leg. An ulcer developed. He applied various ointments to the ulcerated area without success. The ulceration increased in size and became painful. Another smaller ulcer developed below it. The appearance at the time of admission to the New York Hospital in January, 1941, is shown in Fig. 14. The larger ulcer measured 1.5 cm. in diameter. It was in the central portion of an area of dry and thickened skin which covered the outer aspect of the lower one-third of the leg. Numerous telangiectases were in evidence in this area and surface scaliness was excessive. A lesion, typical of psoriasis, showed somewhat higher on the outer aspect of the same leg. The floor of the ulcer was dusky purple in color. Superficial granulations bled easily. The ulcer was very sensitive. There was inguinal adenopathy on both the right and the left sides. None of the other psoriasiform lesions which had been treated showed any evidence of scar or ulcer. At operation the lesion was removed by wide elliptical excision extending down to the fascia and to the periosteum of the fibula. Microscopy showed that this was an epidermoid carcinoma. Biopsy of an inguinal gland showed no regional metastasis. The wound was dakinized and small deep grafts were applied after a period of seven days despite the fact that the granulation tissue never did appear healthy. About one-half of these grafts lived. Subsequently the wound was grafted six times over a period of three months before epithelization was complete. The wound has been healed for four months without recurrence of tumor or ulcer.

The eighth case, like Case 6, is one in which intensive radiation, purposely given, resulted in an apparent arrest of the malignant growth (adenocarcinoma of the ovary, inoperable) but with the late development of ulceration of the entire abdominal wall. Surgical removal of the affected area in this case was more difficult than in Case 6 since the entire thickness of the abdominal wall was involved. This patient, who has gone five years now without sign of recurrence of carcinoma represents, as does the patient in Case 6, an excellent result of x-ray therapy despite the difficult problem presented in the surgical cure of the postradiation ulcer.

CASE 8.—(E. H., N. Y. H. Case 44089.) This case report is that of a 47-year-old unmarried female clerk who was given a total of 17,000 R. of x-ray radiation in six series of treatments, from 1933 to 1935, for inoperable adenocarcinoma of the right ovary. Two years afterward telangiectases appeared over the lower abdominal wall, followed by breaking down of the skin and development of ulceration. Conservative measures were carried out for an eighteen-month period, during which time the epithelium occasionally covered the ulcer only to be followed by recurrent ulceration.

Examination in 1935 showed a deep craterlike ulcer, 13 by 5 cm. in size, over the lower quadrants of the abdomen. This ulcer was floored by pale, gray granulation tissue, hard and fibrotic. For 5 cm. in all directions the tissue adjacent to the ulcer was indurated, thickened, and scarred. On Aug. 2, 1939, this ulcer was excised through a transversely placed elliptical incision. The tissues were ischemic and fibrotic. The floor of the ulcer proved to be only 4 mm. thick, and in the process of excising it the peritoneal cavity was entered. The intestines were adherent to the underside of the abdominal wall. Attempts to close the fibrotic fascia and peritoneum were unsuccessful, and in order to close the defect in the abdominal wall, it was necessary to resort to the use of a rectangular free graft of fascia lata taken from the right thigh. When the peritoneal cavity had been closed in this fashion,

a flap of skin and subcutaneous fat was dissected up from the superior portion of the wound to a point well above the umbilicus. Because of the extensive induration in the femoral and perineal regions, it was not possible to mobilize a flap in the lower part of the wound. By flexing the thighs on the abdomen, that is, putting the patient in a jackknife position, it was possible to close the margins of the wound with deep on-end mattress sutures of dermal gut. This wound subsequently broke down with recurrence of the ulcer. The fascial graft did not slough and the floor of the ulcer presented pale granulation tissue. Dakinization was instituted and a thoracicoepigastric tubed flap[14] was constructed at operation on Oct. 6, 1939.

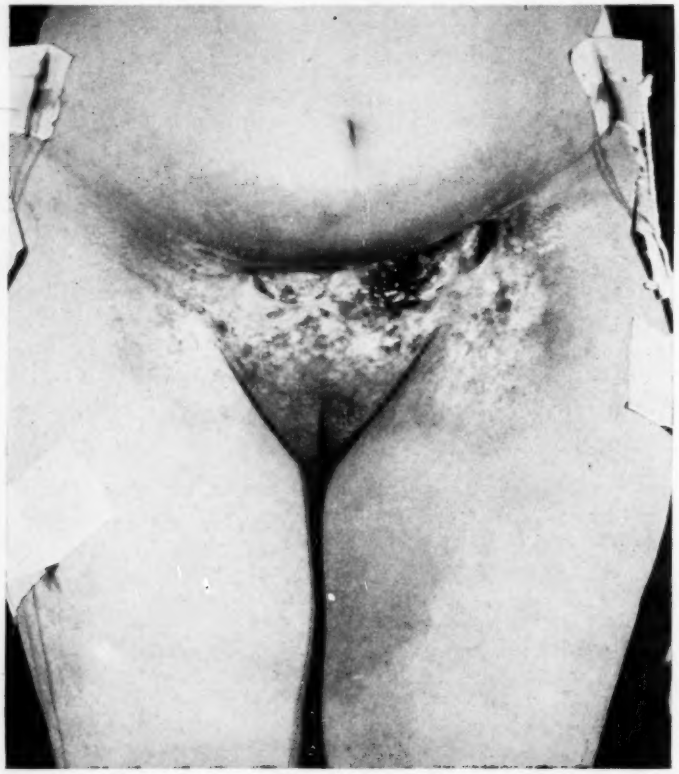

Fig. 15.—Case 8. Photograph showing the painful, deep ulceration of the lower abdominal wall which followed intensive deep radiation given in treatment of inoperable adenocarcinoma of the right ovary. The ulceration extended down into the rectus muscles. There was much brawny edema of the pubic and vulvar tissues. Over these areas the skin was shiny, thickened, and showed alternate areas of pallor due to fibrosis and redness as a result of abundant telangiectases. The floor of the ulcer was pale gray in color. The margins of the ulcer undermined the overlying skin and subcutaneous tissue on all sides. Photograph taken July 31, 1939, four years after the last x-ray treatment had been given and two years after the first sign of ulceration was noticed.

On Nov. 22, 1939, this tube was detached at its upper portion and sutured into the lateral margin of the ulcerated area. Culture from this wound has shown *Streptococcus hemolyticus,* nonhemolytic streptococcus and beta-hemolytic streptococcus. On Dec. 27, 1939, scarred tissue was excised from the midportion of the ulcerated area and a larger section of the tubed pedicle was opened out and sutured into the wound. On Jan. 31, 1940, the remaining ulcerated area over the right lower quadrant of the abdomen was excised and the unused portion of the tube was sutured into this area. The patient was cared for in the dispensary until all sinuses had healed. On May 2, 1940, the tubed pedicle was detached from its point of origin near the iliac spine. Careful microscopic examination of the tissue removed

at operation failed to show evidence of malignant degeneration. Skin, subcutaneous tissue, and rectus muscle were replaced by dense fibrous tissue. There were perivascular collections of lymphocytes and the large number of plasma cells seen in the tissues was striking. The ulcerated area showed necrosis of tissue with polymorphonuclear leucocytes in its upper areas and lymphocytes and plasma cells in

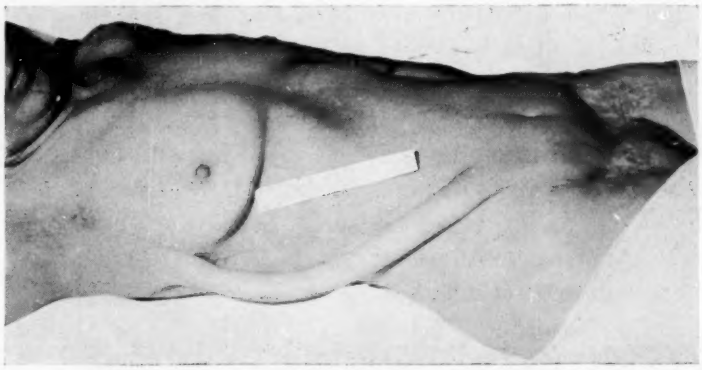

Fig. 16.—Case 8. Photograph taken Nov. 1, 1939, showing the thoracicoepigastric tubed pedicle which was constructed at operation in preparation for surfacing the defect after excision of the ulcer. Tube measured 31 cm. in length. Previous attempt at excision of the ulceration with primary closure had met with failure.

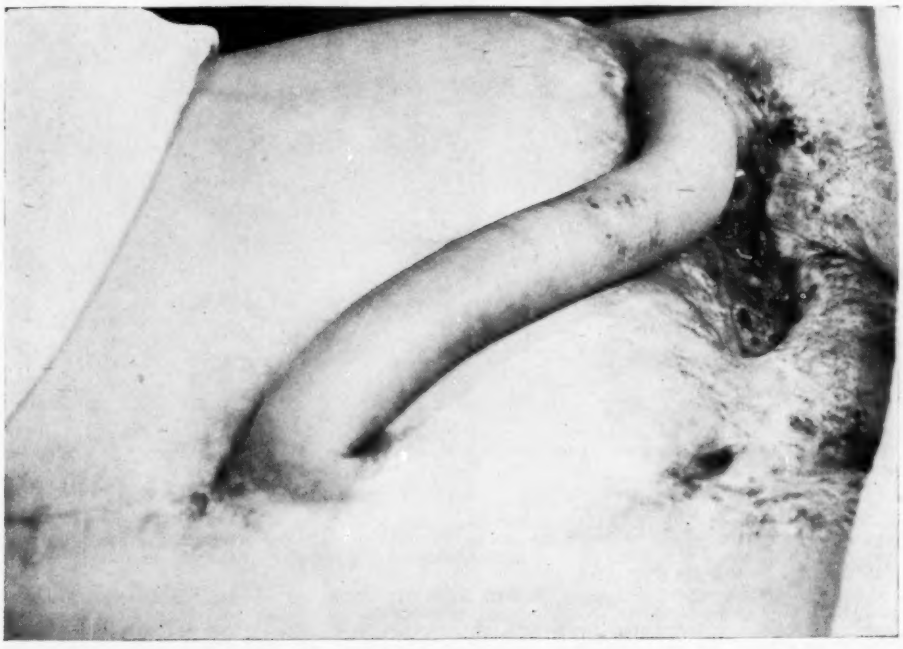

Fig. 17.—Case 8. Photograph taken Dec. 26, 1939, one month after detachment of the upper end of the thoracicoepigastric tubed pedicle and its suture into the left lower quadrant of the abdomen, lateral to the area of ulceration and fibrosis. This view is taken from the right side of the abdomen. After the construction of the tube an interval of forty-seven days elapsed before the upper end was detached and sutured as shown in this photograph.

the fibrous tissue beneath. The accompanying fat showed lymphocytic and plasma-cell infiltration. The microscopic diagnosis was postradiation atrophy of skin and subcutaneous tissues with chronic inflammation and ulceration. The patient has had no further complaints. She was examined in January, 1941, eight months after the

last operation. At that time there was no symptom or sign suggestive of recurrence of the malignancy of the ovary for which this patient was originally subjected to x-ray treatment. Photographs showing the appearance of the ulcerations and the successive stages are shown in Figs. 15, 16, 17, 18, and 19.

The ninth case is an example of the development of carcinomatous ulcer of the finger occurring in a physician who had been exposed to both x-rays and radium over a period of twelve years. The reports of Davis,[15] of Beclere,[16] and of Blair, Brown, and Hamm[17] tell of many other cases in which the physician was the unfortunate victim of the therapeutic measure which he employed. Witwer and Leucutia (1940)[13] reported that of 28 cases of malignancy in x-ray ulcers, 8 occurred on the hands of physicians, surgeons, or dentists. Fortunately, knowledge of the prevention of this development is now in the hands of all who work with x-rays and radium.

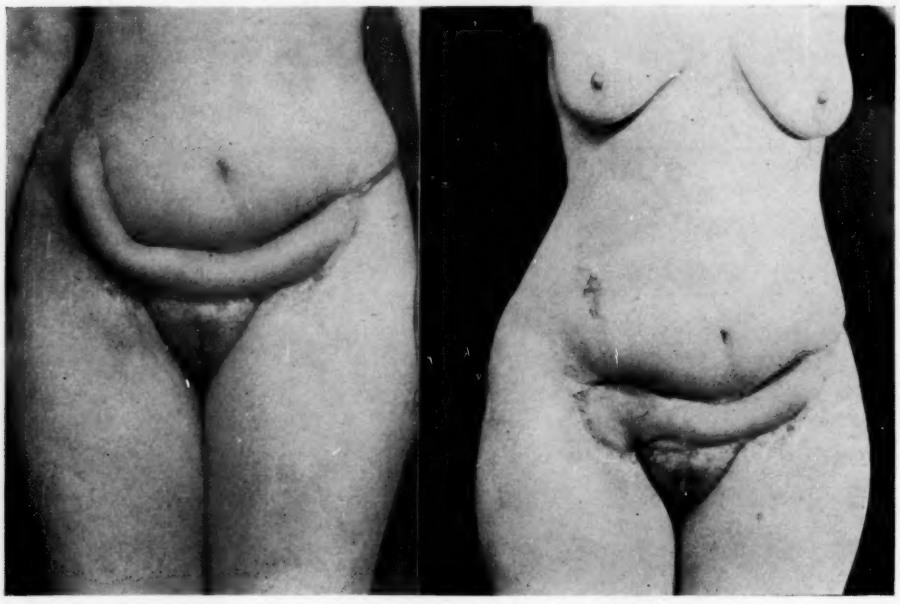

Fig. 18. Fig. 19.

Fig. 18.—Case 8. Photograph taken Feb. 15, 1940, two weeks after excision of the midportion of the ulcer and suture of the tubed flap into the midabdominal and right lower abdominal wall. The flap is still attached by its pedicle to the point of origin just medial to the anterior iliac spine.

Fig. 19.—Case 8. Photograph taken May 23, 1940, three weeks after the detachment of the lower end of the thoracicoepigastric tubed pedicle. This was the final operation. The patient has been followed for eight months following this procedure. There has been no recurrence of ulceration or sinus and there has been no sign of recurrence of the carcinoma of the ovary for which the patient was treated originally.

Case 9.—(N. Y. H. Case 276982.) This case report is that of a 53-year-old surgeon who for twelve years had been exposed to x-rays in fluoroscopic work and to radium in direct application in the practice of his profession. One year before admission to the hospital (Sept. 11, 1940), he noticed crusting of the skin over the distal phalanx of the left middle finger. Several months later the area ulcerated. Subsequently, this area healed only to ulcerate again following the mildest trauma. Four months before admission a small nodule appeared over the middle third of the

same finger on its dorsal radial aspect. This nodule grew slowly in size and two months after its appearance it developed into an ulcer. The lesion was exquisitely tender and gave rise to lancinating pains shooting up the forearm to the elbow.

On examination the lesion presented itself as a punched-out ulcer 3 mm. in diameter with elevated edges through a diameter of 1.2 cm. There was no epitrochlear or axillary adenopathy. Over the dorsal surfaces of the other fingers and thumbs of both hands there were several nontender, firm nodules 2 by 4 mm. in diameter. The finger was amputated at the metacarpophalangeal joint. Microscopic examination of the specimen showed it to be a squamous-cell carcinoma which had not invaded the periosteum or the tendon sheaths. The epidermis was greatly thickened and extremely hyperkeratotic. Chronic inflammatory cells were scattered throughout the corium. The patient has remained well in the five months since amputation of the finger. Artist's sketch of the appearance of the lesion is shown in Fig. 20.

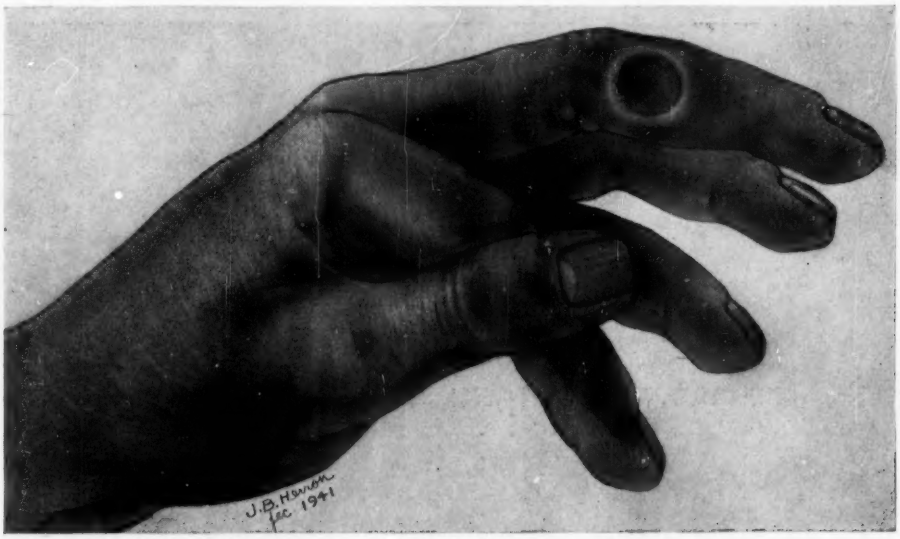

Fig. 20.—Case 9. Painful ulcer of middle finger occurring in a physician who for twelve years had been exposed to x-rays and radium. The lesion proved to be a squamous-cell carcinoma.

The story in the tenth case is regrettable in that malignancy of the skin of the face developed after x-ray treatment for acne. Referring again to the report of Witwer and Leucutia,[13] 3 of 28 cases of roentgen malignancy followed treatment for acne. It seems to me that x-ray therapy is not justified in the treatment of acne not only because of the possibility of the late development of carcinoma, but also because the treatment causes such diffuse scarring of the skin and subcutaneous tissues. Niles[18] has reported clinical experiments in which patients were subjected to x-ray treatment of only one side of the face. His conclusion was that x-ray does not cause fibrosis of the skin of the face when given for acne. However, it is my impression from experience with a great number of patients who sought relief from the deformity presented by scarred skin of the face after x-ray treatment for acne

that the technique of administration of the ray and the response on the part of the tissue is not sufficiently standardized to bear out Niles' conclusions.

CASE 10.—(R. M., N. Y. H. Case 272543.) This case report is that of a 26-year-old American-born girl who had suffered from severe facial acne in the adolescent years. At 13 years of age she was given about twenty x-ray treatments over the nose, cheeks, and chin. These treatments left her with an x-ray burn of the lower face. Later, electrolysis was done by a physician for the removal of hair from the lower face. The patient complained of the tightness, pallor, and shiny appearance of the skin over her nose, cheeks, and chin from the date of completion of the x-ray treatments, but it was not until July, 1939, twelve years after the last x-ray treatment was given, that she noticed a small dark spot on the chin. She traumatized this by squeezing it and subsequently noticed the appearance of many other small grayish black spots in the skin of the chin.

Fig. 21. Fig. 22.

Fig. 21.—Case 10. Basal-cell carcinoma of the chin occurring twelve years after x-ray therapy for acne. Note the cluster of pigmented areas over the left lower chin. These areas varied from 1 to 2 mm. in size and were gray-black in color.

Fig. 22.—Case 10. Result after excision of pigmented areas from right side of chin with primary closure and excision with whole-thickness graft to left side of chin.

On examination the appearance of the patient was as shown in Fig. 21. The skin of the entire face was drawn, thin, and shiny. Over the nose, cheeks, and chin, areas showing loss of normal pigment alternated with areas in which telangiectases were prominent. Over the left side of the chin, extending from the lip obliquely downward and outward, there were twenty minute areas of discoloration. These varied from 1 to 2 mm. in diameter and appeared to be due to grayish black deposit in the corium. Another smaller area under the lower lip on the right showed the same pinpoint, gray-black discolorations. These were believed, at first, to be evidence of traumatic tatoo, possibly due to the electrolysis. Preliminary biopsy on July 17, 1940, showed that this was not so. Microscopic examination of the tissue removed showed scattered areas of metaplastic epithelial cells in the subcutaneous tissue. The microscopic diagnosis was hair matrix carcinoma of the chin. On July 26, 1940,

radical excision of the involved areas was carried out. Elliptical excision on the right side of the chin allowed for primary closure. On the left side of the chin it was necessary to insert a whole-thickness free graft of skin 3.5 by 2 cm. in size. This was taken from the left postauricular area. Postoperative immobilization of the area was accomplished by wiring of the teeth and by a pressure dressing using sponge rubber. There was tremendous edema of the lips in the early postoperative period. This subsided and the graft was a complete success. At no time was there any demonstrable adenopathy in the cervical region. This patient has been followed for twelve months. There has been no evidence of recurrence of the carcinoma. The postoperative appearance is shown in Fig. 22.

DISCUSSION

The cases recorded in this report serve to emphasize the fact that, due to the present widespread application of x-rays and radium, the number of severe postradiation burns, scars, ulcers, and malignant tumors is increasing. These constitute a danger which should not be minimized. Often these aftereffects result in amputation, in complete disability, occasionally in death. It is my firm conviction that x-ray or radium is not justifiable for the treatment of benign lesions when these are of a type and location that make them surgically accessible. The advancement of the principles of plastic surgery and the utilization of these principles in the management of both benign and malignant tumors of the surface of the body will serve to assign a greater percentage of tumors of the skin to the field of surgery. The increase in the number of reported cases in which malignancy has followed the x-ray or radium treatment of inflammatory conditions of the skin is a regrettable circumstance which should be recognized by the profession. It is not my contention that, in the light of present knowledge, all malignant tumors should be treated by surgical excision. A combination of surgery and radiation is certainly desirable. However, radiation in such cases should be given only by competent radiologists who have a full appreciation of the danger of the elements employed.

SUMMARY AND CONCLUSION

Ten case reports are given in which deforming scars, indolent ulcers, or malignancy developed following x-ray or radium therapy. In six of these this therapy was employed for the treatment of benign lesions; of these, two developed x-ray carcinoma. Another case was that of a physician who developed carcinoma of a finger due to excessive exposure to the rays. In three cases, the postradiation ulcers developed after intensive treatment of inoperable malignancy.

Methods of surgical management of these deformities are listed, and examples of many of them are given.

It is concluded that conservative measures are of little value in the eradication of the aftereffects of x-ray and radium and that these lesions

must be treated by surgery. Prevention of the occurrence of these complications of radiation therapy is a goal toward which the medical profession must strive.

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SHOULD THE PLEURAL SPACE BE REDUCED IN SIZE IN THE RESECTION OF LUNG TISSUE?

An Experimental Study*

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INTRATHORACIC operations have enjoyed a high degree of success within recent years. At the present time resection of lung tissue for inflammatory and neoplastic lesions is a commonplace procedure. This marked advance has been due to several factors; namely, improvement in diagnostic methods, better preoperative preparation of the patient, more attention given to postoperative management, and improvement in operative procedures. Many unsolved problems remain in this field of thoracic surgery and in spite of the advancement there is much room for improvement in the present mortality and morbidity.

Clinically, the advisability of obliteration of the pleural space in resection of lung tissue in bronchiectasis and other destructive disease of the chest has long been a question of importance, particularly from the standpoint of the immediate postoperative convalescence and the late effects on the remaining lung tissue.

Many believe it advantageous to prevent overdistention and subsequent fragmentation of the parenchyma by reduction of the pleural space at the time of resection. Further, it is a question as to whether thoracoplasty should accompany or follow total pneumonectomy (Graham,[1] Reinhoff[2]). Such questions arise in the surgical treatment of bronchiectasis, tumors, and other conditions, where a large portion of the total lung is removed. Wound healing, obliteration of the pleural space, residual pneumothorax, cardiorespiratory effort, vital capacity, and the future comfortable existence of the patient may be markedly affected by these factors.

In recent work in this laboratory it was shown that the lung capacity in dogs could be reduced to 15 per cent of its total.[3] This experimental reduction was accomplished over a period of nineteen months by bronchial stenosis and by resection with subsequent stenosis. It was found that the procedure was best tolerated where a four- to six-week interval elapsed between stages of reduction. As a result of the overdistention of the remaining pulmonary tissue marked stretching and fragmentation of the alveolar walls occurred and persisted. In view of

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

*This work was done in part under a grant from The Douglas Smith Foundation for Medical Research of the University of Chicago.

the controversy over the clinical problem it was thought worth while to test the effect of partial obliteration of the residual pleural space on the ultimate physiologic and pathologic alteration of the remaining lung. This obliteration was accomplished by bilateral permanent paralysis, bilateral temporary paralysis, and unilateral permanent and temporary paralysis of the diaphragm. Thoracoplasty in dogs with its difficulty and associated high mortality has not as yet been studied very extensively.

EXPERIMENTAL WORK

Functioning lung tissue was reduced in a total of thirty-three dogs. Twenty-six dogs survived the first operation. These were subjected to a second operation and some of them to further reduction by bronchial stenosis. Various types of phrenic nerve paralyses were done at all operations. Healthy adult mongrel dogs of varying sizes and breeds were used in the work.

PROCEDURE

Lobectomy.—Morphine and atropine were used preoperatively. Intratracheal positive pressure ether anesthesia was used.[4] The technique varied as to the side of the first-stage operation. The approach was made by either dividing or splitting the muscles of the chest. Resections were done through the intercostal space or through a resected rib bed. The lobes were first mobilized by cutting the pulmonary ligament. The pulmonary artery was then isolated and sectioned after a triple ligation; two ligatures proximal and one distal. The pulmonary vein was then isolated and doubly ligated before section. The main bronchus was denuded and a soft right-angled clamp applied after which the lobe or lobes were removed by sharp dissection. The exposed mucosa was painted with a 10 per cent solution of $AgNO_3$ and wiped with alcohol before closure was begun. Interrupted silk sutures were then placed in the bronchial stump. These sutures were numerous enough to occlude the bronchial arteries and to make the bronchus relatively airtight. The stump was then inverted by one or two semi-purse-string sutures of fine silk (Fig. 1). The phrenic nerve was either crushed or a 2 cm. section removed, permitting the diaphragm to rise. The water resistance to outflow from the ether mask was increased slightly (15 to 30 cm. H_2O), to obliterate partially the pleural space before closure was effected. Care was taken never to exceed 20 to 30 mm. Hg wall pressure through the ether machine. Closure was carried out by an interrupted running No. 0 to 00 forty-day chromic catgut suture where the incision was through the resected rib bed; in the interspace incision, two double strands of No. 50 iron-dyed linen pericostal sutures were placed first, after which the interrupted running catgut suture was used. The muscle layers were closed with interrupted catgut sutures, subcutaneous tissue with interrupted fine silk, and the skin with interrupted black silk.

The muscle-splitting incision proved superior in our hands, the closure being more satisfactory and healing taking place with less sinus formation.

The surgical pneumothorax was partially or completely eliminated by use of a pneumothorax machine immediately upon discontinuation of the anesthesia.

The dogs were observed routinely for several hours after operation to note immediate changes. They were then returned to their quarters, no further special care being given. They were observed frequently thereafter for evidence of dyspnea, loss of weight, or any other change.

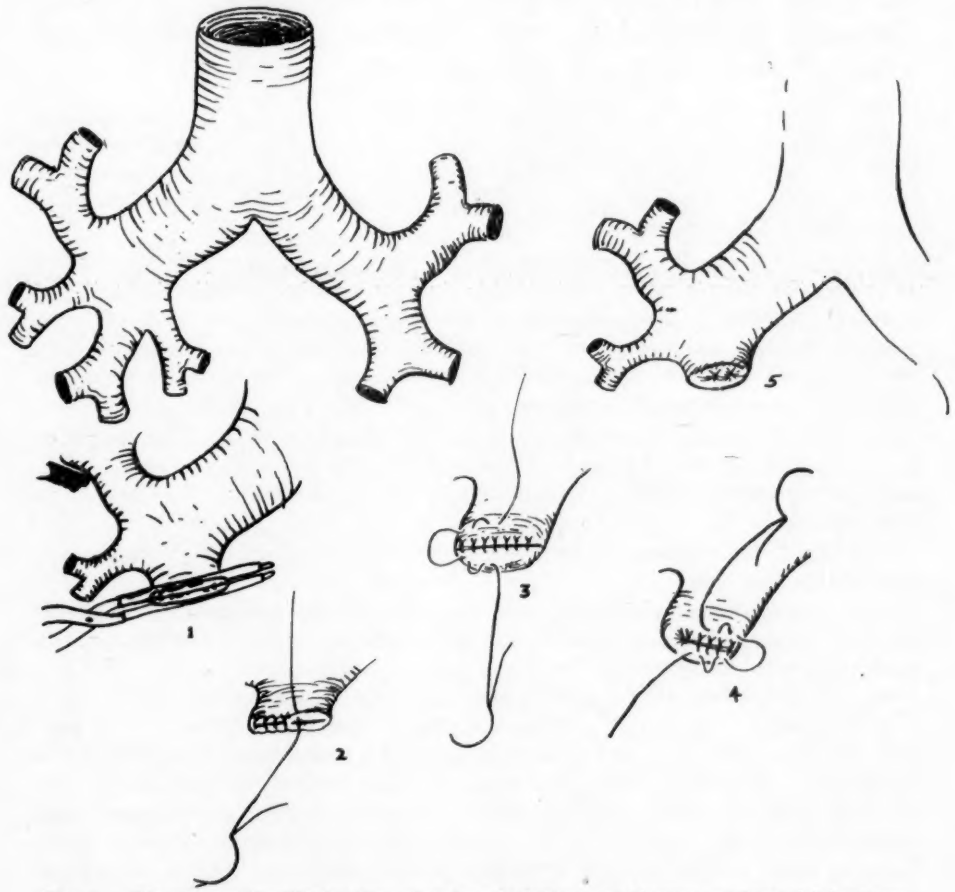

Fig. 1.—Diagrammatic illustration showing technique of closure of bronchial stump.

Bronchial Stenosis.—The dogs were given morphine and atropine before bronchoscopy. Cauterization with a 35 per cent solution of $AgNO_3$ was then done in the manner described by Adams.[5] The bronchus usually closed after one or two applications. The dogs were bronchoscoped routinely at two-week intervals to check closure of the bronchus.

Postoperative Course.—Fluoroscopic and roentgenologic examinations with and without iodized oil were carried out at intervals to study the intrathoracic alterations. Electrocardiograms were also made.

Test of Reserve.—The dogs were exercised by running at intervals to observe signs of respiratory difficulty.

Further tests were carried out with an evacuation chamber into which the dogs were placed. The air pressure was then reduced, thus simulating high altitudes. Readings were made in thousands of feet. The pressure was decreased at the rate of 3,000 to 6,000 feet per minute until the dog lost consciousness. The chamber was then opened and the pressures equalized in one to two minutes.

Animals were sacrificed at various intervals by use of the electric current.[6] Gross alterations of thoracic contents were noted. Specimens of the lung were prepared by drying (air), by the Spalteholtz method of clearing, by Wood's metal casts of the tracheobronchial tree, and by ordinary formalin fixation for histologic study.

PROTOCOL 1.—Dog 917. Healthy dog weighing 12.9 kg.

Reduction of lung function to 38.7 per cent[7] of normal by bilateral operations which were performed seven weeks apart. Three months later this dog was able to tolerate reduction of atmospheric pressure to 502.6 mm. Hg which is equivalent to an altitude of 32,000 feet.[8]

Jan. 12, 1940.—A left lower lobectomy was performed through the sixth interspace and the phrenic nerve crushed. No dyspnea or other complication followed operation. Phrenic function returned in ten weeks as determined by fluoroscopy.

March 7, 1940.—A right lower and accessory lobectomy was performed through the seventh rib bed and the phrenic nerve crushed. After the operation there was slight dyspnea which had disappeared sixteen hours later.

The dog ate poorly for about one week, then gained rapidly. Fluoroscopy on April 17, 1940, showed the lungs aerated. There was no fluid or pneumothorax. The heart was in the midline. The left diaphragm was active; the right showed no active motion.

May 10, 1940.—Bronchography revealed the left upper and right upper and middle lobes aerated.

June 4, 1940.—Fluoroscopy demonstrated no fluid or pneumothorax and that considerable iodized oil remained in the lungs. The heart was in the midline. Both diaphragms were active.

June 5, 1940.—The dog was placed in the evacuation chamber at 11:35 A.M. The air pressure was reduced to 428.8 mm. Hg (15,000 feet altitude) in two minutes. There were no signs of distress and respiration was unchanged. At 411.8 mm. Hg pressure (16,000 feet) there was panting respiration. By 11:39 A.M. the pressure was reduced to 349.2 mm. Hg (20,000 feet). Respiration became slower and deeper at 307.4 mm. Hg (23,000 feet). The dog was in distress, trying to stand, fumbling about and salivating at 225.5 mm. Hg (30,000 feet). He fell over against the drum at 205.8 mm. Hg (32,000 feet) at 11:41 A.M. There was some dyspnea and cyanosis. The pressure was returned to normal at 11:42 A.M. The dog recovered and walked out of the chamber at 11:45 A.M.

June 5, 1940.—Sacrificed. The trachea clamped and chest opened. There was no hydro- or pneumothorax. The remaining lungs were adherent to the lines of incision and were moderately overdistended. The heart showed no abnormalities. See Fig. 6 for histology.

PROTOCOL 2.—Dog 621. A healthy white terrier of 10 kg.

Reduction of lung function to 15 per cent of normal by bilateral operations eleven weeks apart, plus additional collapse by bronchial stenosis. Bilateral permanent

diaphragmatic paralysis accompanied the operations. About three months later the dog was able to tolerate a reduced pressure of 282 mm. Hg (25,000 feet) without loss of consciousness.

Aug. 10, 1939.—A right lower and accessory lobectomy was performed and the phrenic nerve sectioned. There was no dyspnea or other abnormal effect. The dog ate and was in good condition two days later.

Oct. 14, 1939.—Fluoroscopy revealed the chest cage aerated bilaterally. The right diaphragm showed no active motion. General condition was good.

Oct. 30, 1939.—A left lower lobectomy was performed through the sixth interspace and the phrenic nerve sectioned. Some difficulty was had uniting the anterior intercostal wound so that an astonishing degree of subcutaneous emphysema developed on the dog's left side. This extended even down the left leg. The dog was quite dyspneic at the end of operation but improved slightly after removal of 200 c.c. of air from the left chest. No air was found in the right chest. The condition was considered poor. There was marked improvement in twenty-four hours and no difficulty thereafter.

Jan. 5, 1940.—Fluoroscopy and bronchograms revealed the three remaining lobes filling the pleural space. Both diaphragms were paralyzed. (Fig. 3*A*.)

Feb. 3, 1940.—Bronchoscopy. A 35 per cent solution of $AgNO_3$ was applied to the left upper lobe bronchus. The general condition was good.

Feb. 17, 1940.—Bronchoscopy. The left upper lobe bronchus was closed.

March 3, 1940.—Bronchoscopy. The right middle lobe bronchus was cauterized.

March 19, 1940.—Bronchoscopy. The right middle lobe bronchus was closed. Only the right upper lobe bronchus remained open.

April 17, 1940.—Fluoroscopy. The right chest was well aerated. The diaphragms were motionless, the left higher than right. The left upper thoracic region was dense.

May 3, 1940.—Bronchograms showed the right upper lobe aerated (Fig. 3*B*).

June 5, 1940.—The dog was placed in the evacuation chamber at 3:49 P.M. Some respiratory difficulty was exhibited at 395.4 mm. of Hg (17,000 feet). The dog was uneasy at a pressure of 364 mm. of Hg. (19,000 feet). There was slight dyspnea at 349.2 mm. of Hg (20,000 feet) and this was more marked at 282 mm. of Hg. (25,000 feet). The dog was unsteady, moved slowly about the cage. He fell down at 25,000 feet but was not unconscious. There was some cyanosis at 3:54 P.M. Pressure off at 3:55 P.M. The dog was out and walking about normally at 3:57 P.M.

This dog was not taken up faster or farther because he was not to be sacrificed.

June 21, 1940.—The dog was in good health. The respiratory effort suggested that the dog was dyspneic, but there was no cyanosis. He was unable to pant. (Dog 30 had same type of respiration.)

February, 1941.—This dog, No. 621, has remained in good health to date. At rest he still appears dyspneic due to the peculiar intercostal type of breathing. There is no cyanosis evident except on extreme exercise.

RESULTS OF EXPERIMENTS

The experimental work on the series of twenty-six dogs is presented in Table I. The dogs have been grouped according to the degree of obliteration of pleural space and to the amount of reduction in lung function beyond the two-stage operation. From a study of the chart it is apparent that Groups I, II, and VI represent primarily a study of the effect of varying degrees of reduction in pleural space; whereas, Groups III, IV, and V are a comparative study of various degrees of reduction in lung tissue or function.

TABLE I

REDUCTION IN LUNG FUNCTION WITH OR WITHOUT OBLITERATION OF RESIDUAL PLEURAL SPACE IN 26 DOGS

GROUPS SHOWING TYPE OF PHRENIC PARALYSIS REDUCTION BY STENOSIS	DOGS IN GROUP	BILATERAL OPERATION	ADDITIONAL REDUCTION
I. Bilateral permanent paralysis*	7	7	0
II. Unilateral permanent paralysis and unilateral temporary paralysis	2	2	1 (operative)
III. Unilateral permanent paralysis and sublethal reduction	4	4	2
IV. Unilateral permanent, unilateral temporary paralysis and sublethal reduction	3	3	3
V. Bilateral permanent paralysis and sublethal reduction	4	4	4
VI. Bilateral temporary paralysis	6	6	0

*Seven dogs not included in this group died after the first-stage operation from various causes (see text).

Table II shows in some detail the work on twenty-six individual dogs. The general grouping presented in Table I is followed. The reduction by operative stages and by bronchial stenosis is presented and the intervals between reduction are shown. These vary from three (Dog 939) to fourteen weeks (Dog 871). The causes of death or other end results are shown.

Group I.—Bilateral permanent paralysis of the diaphragm and reduction of lung function to 38.7 per cent of normal. Seven dogs are included in this group. The dogs had bilateral operations removing the left lower and right lower and accessory lobes. Phrenicectomy was performed at both operations. The average length of time between operations was sixty-nine days. Two operative deaths occurred from asphyxia, one due to a surgical pneumothorax and the other to the pre-existing fibrosis and atelectasis on the left upper lobe which was found at autopsy. Two deaths occurred twenty-four hours after operation due to distemper which had been present at the time of the second operation. Three dogs were sacrificed several months after the second operation. Their reaction to rarified atmosphere seemed normal.

Group II.—Unilateral permanent and temporary paralysis of the diaphragm and reduction of lung function to 38.7 per cent of normal. The average time between operations was sixty-nine days. It will be noted that dog 867 had a more extensive reduction at the first stage than usual, the right middle, lower, and accessory lobes being removed. Phrenicectomy was done. Five weeks later the left lower lobe was removed and the phrenic nerve crushed. This dog's postoperative course was not unusual aside from some coughing several weeks after operation. This we believed to be due to the loosening of bronchial sutures since bronchoscopy and x-ray examination revealed no other cause. The bronchial tree was well outlined by iodized oil (Fig. 2). About three

months after the second-stage operation the left diaphragm had recovered its function. Five months after the last operation the left upper lobe was removed. The dog had no difficulty during the operation which was easily done. Afterwards, the respirations were deeper than normal. No cyanosis was present at any time. A temporary cardiac irregularity developed and an electrocardiogram was taken. This showed a tendency to premature auricular contractions and alternating extrasystoles. There was a tendency to slight left axis deviation. The dog did very well for one week and then suddenly began vomiting all food. He died on the twelfth postoperative day. At autopsy the lower third of the esophagus was markedly dilated. The left chest was free of fluid and air and the incision was well healed. The right upper lobe filled the upper portion of the left chest.

Group III.—Unilateral permanent paralysis of the diaphragm and reduction of lung function to 15 per cent of normal. The average time between operations was fifty-four days. Four dogs are shown. Dog 602 died after the second operation and at autopsy the right middle and upper lobes were atelectatic. Dog 612 was in a poor nutritional state and failed to survive the second operation. At autopsy a small empyema was found on the right side. Two dogs were reduced to one lobe.

Group IV.—Unilateral permanent and temporary paralysis of the diaphragm with reduction of lung function to 15 to 30 per cent of normal. The average time between operations was eighty-five days. Three dogs are shown and all had bronchial stenosis. Dog 636 was bronchoscoped on several occasions with cautery of the left upper lobe bronchus which failed to close. At autopsy this lobe was found to be consolidated. The lung function of Dog 687 was reduced to one lobe. He died following bronchoscopy about one week after the right middle lobe was closed. The dog had not seemed unusual and at autopsy there was no apparent cause of death. Dog 869 was reduced to two lobes but was unable to tolerate bronchoscopy after the preoperative sedation. Extreme cyanosis developed on several attempts.

Group V.—Bilateral permanent paralysis of the diaphragm and reduction of lung function to 15 per cent of normal. The average interval between operations was fifty-eight days. Four dogs are presented. There were two distemper deaths, one and two weeks after the final cauterization. One dog (No. 30) was sacrificed and one (No. 621) is living.

Group VI.—Bilateral temporary paralysis of the diaphragm and reduction of lung function to 30 per cent of normal. The time between operations was thirty-six days, the interval on the last two dogs being 22 days. Two dogs were sacrificed several months after the second stage operation, Dog 886 having had an additional thoracotomy for crushing the right phrenic nerve, which was not done at the second operation.

TABLE

EXPERIMENTAL

GROUPS	FIRST-STAGE OPERATION							SECOND-STAGE	
	DOG NO.	RESECTED		PHRENIC		RESULT		RESECTED	
		LOBES	DATE	CUT	CRUSH	WELL	DIED	LOBES	DATE
I. Bilateral, permanent paralysis	447	Left lower	4/ 6/39	+		+		Right lower and accessory	7/25/39
	518	Left lower	5/ 3/39	+		+		Right lower and accessory	8/28/39
	871	Right lower and accessory	12/18/39	+		+		Left lower	3/ 5/40
	892	Right lower and accessory	12/27/39	+		+		Left lower	3/ 6/40
	972	Right lower and accessory	2/ 9/40	+		+		Left lower	3/27/40
	3	Right lower and accessory	2/16/40	+		+		Left lower	3/20/40
	993	Right lower and accessory	3/ 2/40	+		+		Left lower	3/28/40
II. Unilateral permanent and unilateral temporary paralysis	637	Right lower and accessory	9/29/39	+		+		Left lower	1/ 4/40
	867	Right lower and accessory middle	12/13/39	+		+		Left lower	1/23/40
III. Unilateral permanent paralysis and sublethal reduction	602	Right lower and accessory	7/31/39	+		+		Left lower	11/16/39
	612	Right lower and accessory	8/ 4/39	+		+	+	Left lower	11/ 1/39
	635	Right lower and accessory	8/31/39	+		+		Left lower	11/10/39
	695	Right lower and accessory	9/18/39	+		+		Left lower	11/14/39
IV. Unilateral permanent and unilateral temporary paralysis and sublethal reduction	636	Right lower and accessory	9/21/39	+		+		Left lower	1/ 8/40
	687	Right lower and accessory	9/27/39	+		+		Left lower	1/10/40
	869	Right lower and accessory	12/15/39	+		+		Left lower	1/24/40
V. Bilateral permanent paralysis and sublethal reduction	449	Left lower	4/26/39	+		+		Right lower and accessory	7/18/39
	30	Right lower and accessory	2/16/40	+		+		Left lower	3/20/40
	31	Right lower and accessory	2/19/40	+		+		Left lower	3/27/40
	621	Right lower and accessory	8/10/39	+		+		Left lower	10/30/39

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TABLE
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TUDIES

...ATION				FURTHER REDUCTION		REMARKS
PHRENIC		RESULT		STENOSIS		
...UT	CRUSH	WELL	DIED	LOBES	DATE	
+			+			Died when anesthesia was discontinued; operative
+			+			Died when anesthesia was discontinued; left upper lobe atelectatic; operative
-		+				6/5/40: evacuation chamber, 30,000 ft.; sacrificed
+		+				Died 3/7/40; right middle and part of left upper lobes consolidated; distemper
+		+				Died 3/28/40; right middle and part of left upper lobes consolidated; distemper
-		+				6/10/40: evacuation chamber, 25,000 ft.; sacrificed
-		+				6/5/40: evacuation chamber, 32,000 ft.; sacrificed
	+	+				6/5/40: evacuation chamber, 31,000 ft.; sacrificed
	+	+		Left upper lobectomy	6/19/40	Died 7/1/40; dilatation of esophagus with vomiting
			+			Died when anesthesia was discontinued; atelectasis of right middle and tension pneumothorax; operative
			+			Died as operation was being completed; emaciated and had small empyema on right; operative
		+		Left upper to 1 mm. Right middle	5/ 6/40 5/31/40	Killed in evacuation chamber at 26,500 ft. 6/5/40
		+		Left upper Right middle	2/ 3/40 3/ 2/40	6/7/40; evacuation chamber, 26,000 ft.; sacrificed
	+	+		Left upper failed to close Right middle	 3/19/40	6/20/40: sacrificed
	+	+		Left upper Right middle	3/19/40 3/19/40	Died 3/25/40, no apparent cause; pneumothorax?
	+	+		Left upper	5/16/40	6/21/40: evacuation chamber, 24,500 ft.; sacrificed
		+		Left upper Right middle	10/7/39	Died 11/18/39, two weeks after last cauterization Right upper and right middle consolidated; distemper
		+		Left upper Right middle	5/ 6/40 5/31/40	6/20/40: sacrificed
		+		Left upper		Died 5/1/40, one week after last cauterization; right upper, right middle, and part of left upper consolidated; distemper
		-		Left upper Right middle	2/17/40 3/19/40	Evacuation chamber, 25,000 ft.; living

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TABLE—CONT'D

GROUPS	FIRST-STAGE OPERATION							SECOND-S	
	DOG NO.	RESECTED		PHRENIC		RESULT		RESECTED	
		LOBES	DATE	CUT	CRUSH	WELL	DIED	LOBES	DA
VI. Bilateral temporary paralysis	917	Left lower	1/12/40		+	+		Right lower and accessory	3/
	886	Left lower	1/22/40		+	+		Right lower and accessory	3/2
	156	Right lower and accessory middle	5/ 9/40		+	+		Left lower	6/1
	186	Right lower and accessory middle	5/10/40		+	+		Left lower	6/1
	180	Right lower and accessory middle	5/22/40		+	+		Left lower	6/1
	939	Right lower and accessory middle	5/23/40		+	+		Left lower	6/1

The remaining four dogs were subjected to a trilobectomy at the first operation, and a second-stage left lower lobectomy about three weeks later. The left diaphragm of these dogs was not paralyzed. Their postoperative courses differed in no way from other dogs in the series. At a later date we plan to resect the left upper lobe and crush the phrenic nerve.

There were seven dogs which died after the first-stage operation. The causes of these deaths were as follows: two of wound infection and pneumothorax, two of distemper, one of erosion of an intercostal vessel causing fatal hemorrhage (this was at the site of the pericostal suture), one due to a gross bilateral empyema, and one operative death due to a needle puncture of the middle lobe. In the latter the pneumothorax could not be controlled and the dog died later during a reoperation in an attempted middle lobectomy.

It is obvious that these seven dogs represent the mortality for the entire series as regards survival of the first-stage operations; no other early deaths occurred.

Table III shows the immediate effects, late physiological and physical effects, and gross and microscopic findings after obliteration of the pleural space by phrenic nerve interruption. Diaphragmatic paralysis was permanent, temporary, and combined in character. As indicated, more marked gross overdistention of the remaining lung occurred in dogs with the temporary paralysis. On microscopic examination the most extreme degree of change was found in dogs with permanent paralysis. This change was in the terminal respiratory units.

Table IV shows the immediate and late effects of varying degrees of reduction in functioning lung. The causes of death are also indicated.

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TABLE—CONT'D

COND-ITION	RATION				FURTHER REDUCTION		REMARKS
TED	PHRENIC		RESULT		STENOSIS		
DATE	CUT	CRUSH	WELL	DIED	LOBES	DATE	
3/7		+	+				6/5/40: evacuation chamber, 32,000 ft.; sacrificed
3/21			+		Phrenic crushed	4/11/40	6/7/40: sacrificed
6/13			+				Living
6/14			+				Living
6/14			+				Living
6/14			+				Living

IMMEDIATE EFFECTS

The immediate effects of reduction of lung function are presented in Tables III and IV. There was no cardiorespiratory embarrassment following bilateral resection of lung tissue or with additional reduction by bronchial stenosis, with the following exceptions: Dog 993 developed a cardiac irregularity and cessation of the heart beat during operation. An injection of 1 c.c. of 1:1,000 adrenalin intracardially was followed by recovery; Dog 636 was rather dyspneic for twenty-four hours after the second operation; Dog 621 exhibited marked dyspnea associated with an extensive subcutaneous emphysema on the left side, both persisting for twenty-four hours.

A tendency to gastric dilatation immediately following phrenic nerve paralysis necessitated decreasing the intratracheal positive pressure and in a few instances required postoperative aspiration of air from the stomach. The diaphragm was elevated and immobile when crushed or sectioned.

The sequence and interval between operations varied. In several dogs only one lobe was removed at the first operation, and two lobes at the second operation. In the majority of the animals, however, the sequence was reversed, the larger amount of lung being removed at the first operation. In general this latter procedure was more easily tolerated.

The interval between operative stages varied from three weeks to four months. If, following the first stage, the animal remained in a good nutritional state, and without complications, the second stage was as well tolerated in three weeks as in four months.

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TABLE III

EFFECT OF OBLITERATION OF RESIDUAL-PLEURAL SPACE FOLLOWING REDUCTION OF FUNCTIONING LUNG

REDUCTION OF PLEURAL SPACE	NO. OF DOGS	IMMEDIATE EFFECTS	PHYSICAL AND PHYSIOLOGICAL EFFECTS	GROSS PATHOLOGY	MICROSCOPIC PATHOLOGY
Permanent	11	1. Temporary dilatation of stomach on paralysis of phrenic nerve 2. No cardiac embarrassment 3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax	1. Diaphragms elevated and immobile 2. No dyspnea or cyanosis on exercise excepting one-lobe dogs 3. Normal reaction to rarified atmosphere 4. Healthy 5. Change of respiration from abdominal to thoracic type 6. No cardiac embarrassment 7. EKG normal	1. Adhesions between lung and incision 2. Moderate overdistention of lung 3. Upper lobe herniation through mediastinum in one-lobe dogs 4. Lung spongy in appearance; honey-combed on section 5. Heart normal	1. Definite emphysema found in one-lobe dogs 2. Dilatation and disruption, especially the alveolar ducts and sacs in one-lobe dogs 3. Bronchi dilated, particularly terminal portions 4. Some breakdown and stretching of alveolar walls in one-lobe dogs 5. No connective or elastic tissue increase; some disruption in one-lobe dogs
Partial permanent and temporary	9	1. Temporary dilatation of stomach on paralysis of phrenic nerve 2. No cardiac embarrassment 3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax	1. Temporary elevation of diaphragm with regeneration in 2 or 3 mo. 2. No dyspnea or cyanosis on exercise 3. Normal reaction to rarified atmosphere 4. Healthy 5. No significant change in type of respiration 6. No cardiac embarrassment 7. EKG normal	1. Adhesions between lung and incision 2. Increased overdistention of lung 3. Upper lobe herniation through mediastinum in one-lobe dogs 4. Lung spongy in appearance; honey-combed on section 5. Heart normal	1. No emphysema 2. Dilatation of terminal respiratory units 3. Bronchi dilated, particularly terminal portions 4. Some stretching of alveolar walls—no disruption 5. No connective or elastic tissue increase; stretching but less disruption in one-lobe dogs
Temporary	6	1. Temporary dilatation of stomach on paralysis of phrenic nerve 2. No cardiac embarrassment 3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax	1. Temporary elevation of diaphragm with regeneration in 2 or 3 mo. 2. No dyspnea or cyanosis on exercise 3. Normal reaction to rarified atmosphere 4. Healthy 5. Change of respiration from abdominal to thoracic type during paralysis 6. No cardiac embarrassment 7. EKG normal	1. Adhesions between lung and incision 2. Marked overdistention of lung 3. Lung spongy in appearance; honey-combed on section 4. Heart normal	1. No emphysema 2. Dilatation of terminal respiratory units 3. Bronchi dilated, particularly terminal portions 4. Some stretching of alveolar walls—no disruption 5. No connective or elastic T increase; stretching but no disruption

TABLE IV

COMPARATIVE STUDY OF VARYING DEGREES OF REDUCTION OF FUNCTIONING LUNG TISSUE

REDUCTION TO	METHOD	NO. OF DOGS	IMMEDIATE EFFECTS	LATE EFFECTS	CAUSE OF DEATH				
					OPERATIVE	DISTEMPER	OTHER CAUSES	SACRIFICED	LIVING
Three lobes	Resection	12	No cardiorespiratory embarrassment except Dog 993; tendency to gastric dilatation upon paralysis of diaphragm; slight dyspnea	Reserve: Dyspnea { at rest—none on exertion—slight Rarified atmosphere—normal EKG—normal Nutritional state—good Air passages and cells—dilated	4	2		6	
Two lobes	Resection	4	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; slight dyspnea	Dyspnea { at rest—none on exertion—slight EKG—normal Air passages and cells—dilated					4
	Resection and stenosis	4	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; slight dyspnea	Dyspnea { at rest—none on exertion—slight Rarified atmosphere—almost normal EKG—normal Air passages and cells—dilated		2		2	
One lobe	Resection	1	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; Dog 867, dyspnea for twenty-four hr.	Dyspnea { at rest—none on exertion—moderate EKG—temporary cardiac irregularity Dilatation of esophagus—caused death			1		
	Resection and stenosis	5	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; Dog 621, dyspnea for twenty-four hr.	Dyspnea { at rest—none on exertion—moderate Rarified atmosphere—almost normal EKG—normal Compensatory emphysema—present		1		3	1

LATE EFFECTS

Respiratory Reserve.—While at rest there were no manifestations of diminished respiratory reserve. Dogs 621 and 30, after having permanent paralysis of the diaphragms and reduction of lung function to 15 per cent (one lobe), had an apparent increase in respiratory effort. An interesting observation was their inability to pant. They were never found to be cyanotic.

TABLE V

RESPIRATORY RESERVE AT REST AS DETERMINED BY REDUCTION OF ATMOSPHERIC PRESSURE

STANDARD ATMOSPHERIC PRESSURE		CONDITION OF ANIMAL AND PER CENT OF FUNCTIONING LUNG	NO. OF DOG	ALTITUDE TOLERATED	TIME OF ASCENT (MIN.)	AVERAGES	
ALTITUDE (FT.)	PRESSURE (MM. HG)					ALTITUDE (FT.)	PRESSURE (MM. HG)
0	760.0	Normal (6 lobes) 100%	1	30,500	10	30,400	221.6
1,000	733.0		2	30,500	10		
5,000	632.4		3	29,500	10		
10,000	522.6		4	32,000	8		
15,000	428.8		4	29,500	11		
20,000	349.2	3 lobes 38%	917	32,000	6	30,000	225.6
25,000	282.0		993	32,000	7		
30,000	225.6		3	25,000	7		
35,000	178.7		637	31,000	9		
40,000	140.7		871	30,000	9		
		2 lobes 23%	636	27,500	4	26,000	269.8
			869	24,500	6		
		1 lobe 15%	635	26,500*	5	25,833	272.0
			621	25,000†	6		
			695	26,000	10		

*Failed to recover.
†Did not become unconscious.

While at rest the dogs were put into an evacuation chamber and subjected to rapid diminution of the atmospheric pressure. The results of these tests are presented in Table V. The reduction in atmospheric pressure is indicated in mm. of Hg and the corresponding altitude levels.[8] No appreciable increase in respiratory effort was noted in dogs which had a marked reduction of functioning lung. In general they were able to tolerate almost as much decrease in atmospheric pressure as were normal control dogs.

The dogs tolerated moderate exercise very well. Dogs which ran about much or were excited did not become cyanotic. Dog 869, referred to in Table II, Group IV, was quite dyspneic on exercise. He was able to tolerate a pressure of only 288.2 mm. of Hg (24,500 feet) in the evacuation chamber.

Pneumothorax.—Partial obliteration of the surgical pneumothorax immediately after the operation eliminated early respiratory embarrassment and contributed much toward lowering the operative mortality. It is not likely that all the residual air was removed, but in no dog was

pneumothorax observed after the immediate postoperative period. In the previous work referred to spontaneous pneumothorax was observed on numerous occasions when reduction of the lung function was accomplished by bronchial stenosis. It was noted on the side of greatest collapse. We had no case of spontaneous pneumothorax, although it was suspected in Dog 687. Large emphysematous bullae were found at autopsy in several instances however. These were in the one- (15 per cent) or two- (30 per cent) lobe dogs, No. 695 in particular. In one instance a large bulla was found in a three-lobe (38.7 per cent) dog (No. 886).

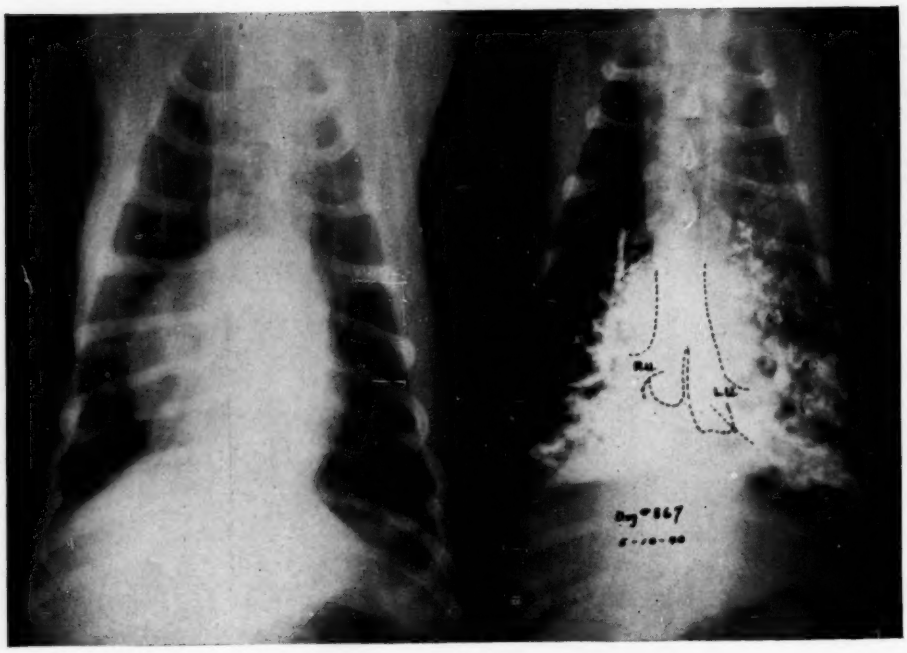
Permanent bronchial closure was routinely obtained by the method described. At autopsy the stumps were firmly healed, although suture material persisted in some cases.

Cardiac Phenomena.—No cardiac irregularities were noted except in Dog 867 as described above. The electrocardiograms were normal. At autopsy, no gross cardiac abnormalities were found.

Diaphragms.—Frequent fluoroscopic and roentgenologic examinations were made in order to note intrathoracic changes and recovery of diaphragmatic function. The diaphragms were elevated and immobile or the motion paradoxical in cases of unilateral paralysis. Fluoroscopic and x-ray studies of the diaphragms showed the following: (1) In permanent paralysis the diaphragm was usually elevated to the eighth interspace. (2) In temporary paralysis, after recovery of function, the elevation was usually at the ninth rib. (3) Where no paralysis was produced the diaphragm was usually located at the tenth rib. In general the elevation varied directly with the degree of reduction of lung function. When temporarily paralyzed diaphragmatic function returned in two to three months. Normal respiration in the dog is largely abdominal in type. As paralysis was carried out thoracic breathing was more noticeable. When both phrenics were interrupted breathing seemed changed completely, the dog appeared dyspneic, respiration labored and diminished. These dogs did not pant nor were they cyanotic even when exercising. The nutritional state remained good throughout the experimental period with two exceptions (Dogs 30 and 612). In many instances the animals gained weight. An open empyema was present in Dog 637, but this did not affect the dog's weight.

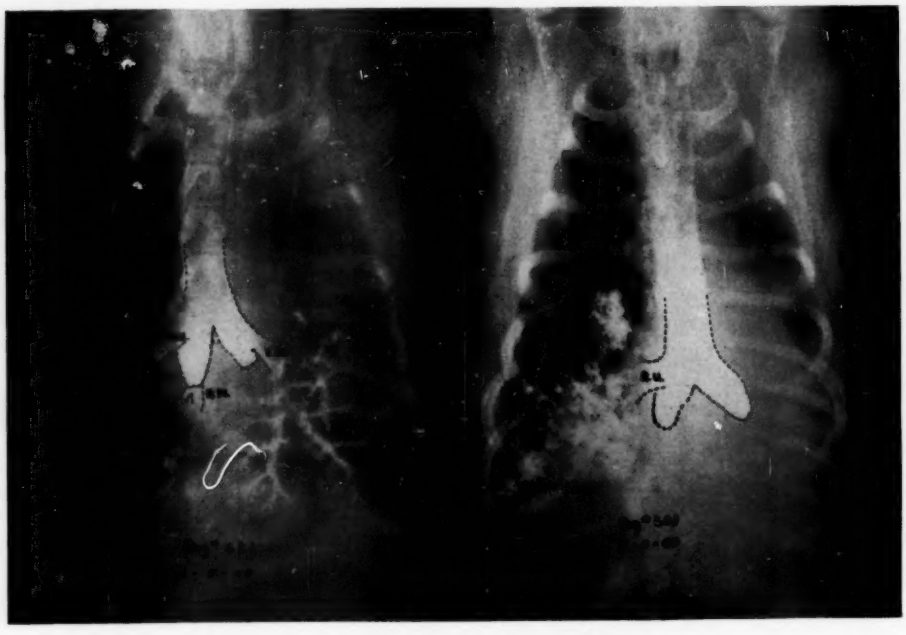
On physical examination there was dullness to percussion over the atelectatic lobes. Where the lung function was reduced to one lobe (15 per cent) the heart was usually palpable immediately beneath the chest wall on the opposite side. This finding was verified on fluoroscopy and at autopsy. The remainder of the chest was usually hyper-resonant.

Fluoroscopy revealed a decreased density of the overdistended lung and the deviation of the mediastinum with its contents, especially in one-lobe dogs, the superior portion often reaching the opposite chest wall. In several cases the right heart seemed slightly dilated.



A. *B.*

Fig. 2.—Dog 867 before (*A*) and after (*B*) introduction of iodized oil. The lung function had been reduced by bilateral operation to the two upper lobes (30 per cent of normal).



A. *B.*

Fig. 3.—Dog 621. Bronchograms. *A*, After reduction of function to three lobes (38.7 per cent of normal) by bilateral operation; *B*, after further reduction of function to the right upper lobe (15 per cent of normal) by bronchial stenosis. Bilateral permanent paralysis of diaphragms.

In general, x-rays agreed with fluoroscopic findings. Iodized oil injections were made to outline the tracheobronchial tree in its altered status. (Figs. 2 and 3.)

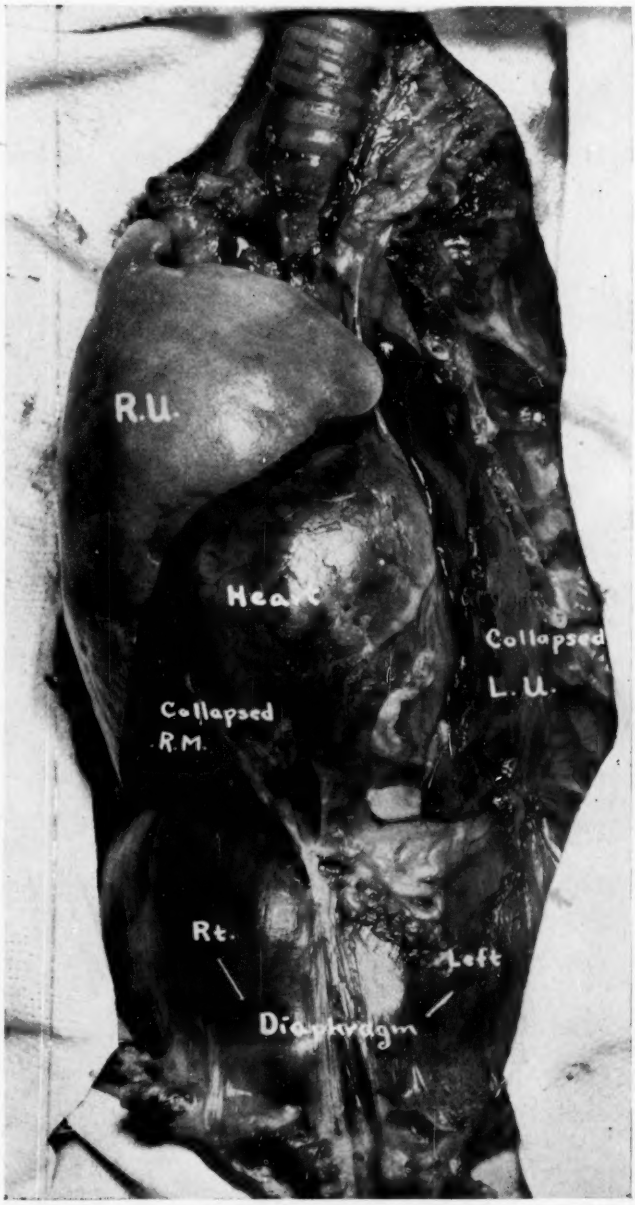
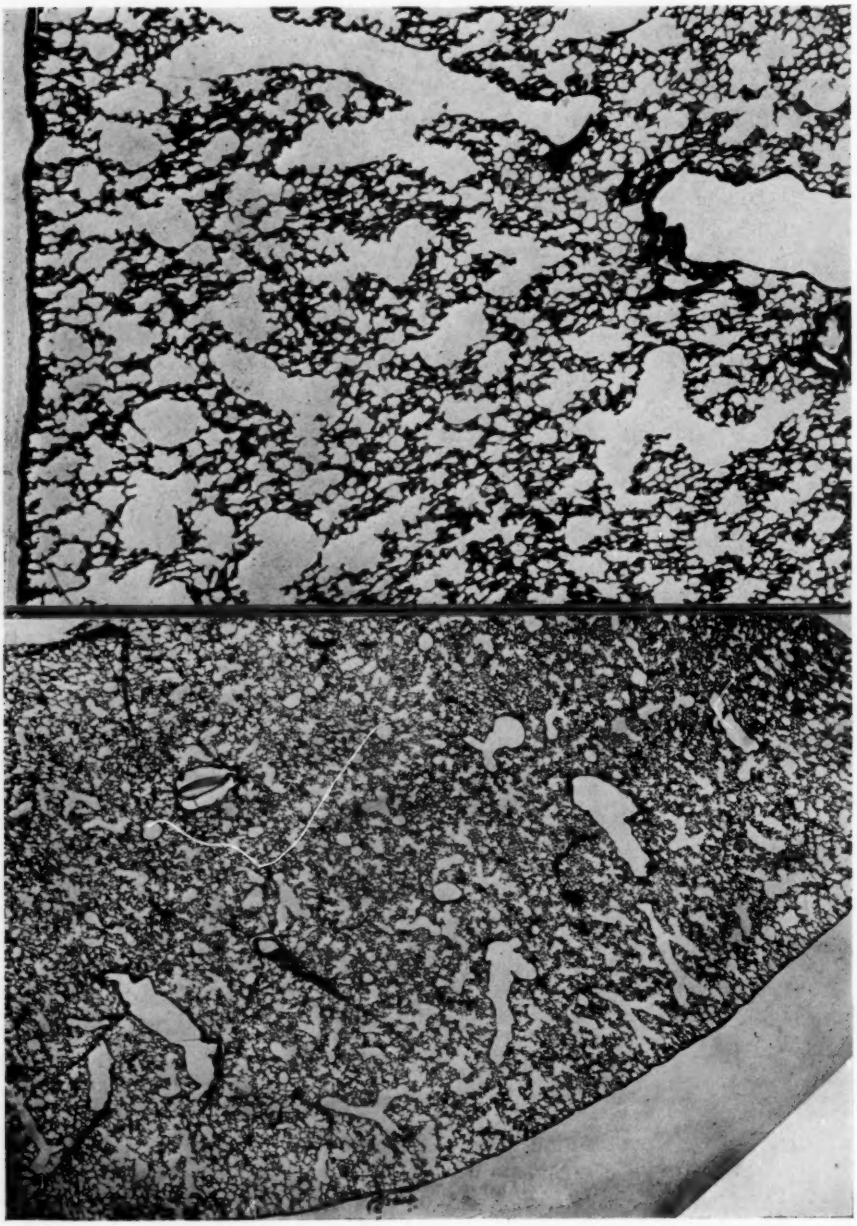


Fig. 4.—Dog 687. Autopsy specimen showing reduction of function to right upper lobe (15 per cent of normal) showing marked overdistention with herniation into the left chest.

In all two- or three-lobe dogs the mediastinal structures remained in the midline; whereas, in one-lobe dogs the heart was always deviated to the opposite side. There was some rotation of the air passages as demonstrated by the bronchograms.

PATHOLOGY

Gross.—The remaining inflated lung was usually found adherent to the healed lines of incision. As a rule there was no fluid in the pleural space although a few cubic centimeters were found in some dogs. The lungs routinely showed overdistention, the extent dependent upon two factors: paralysis of the diaphragm and the degree of reduction of functioning lung tissue. This was most extreme in one-lobe dogs and in those instances where the diaphragms were temporarily paralyzed.



B.

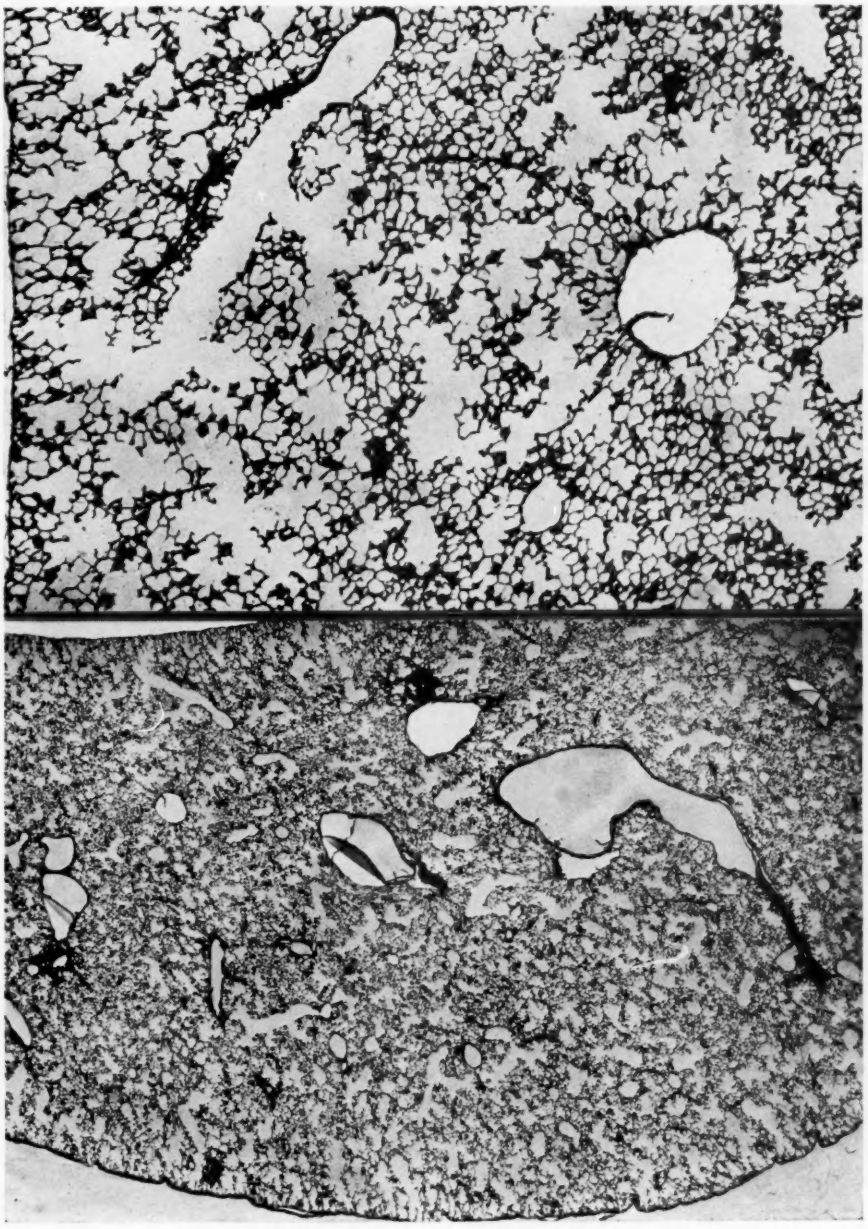
A.

Fig. 5 *A* and *B*.—Dog 3. Bilateral permanent paralysis of diaphragm. Microscopic appearance of aerated lung three months after reduction of lung function to three lobes (38.7 per cent). Note dilatation of terminal respiratory units. No emphysema demonstrable. Magnification ×7 and ×20.

Where only one lobe remained there was herniation of the lung into the opposite pleural cavity (Fig. 4). This was accompanied by deviation of the heart. There was no demonstrable evidence of hypertrophy or dilatation of the cardiac chambers. The diaphragms were definitely elevated in cases of paralysis.

The lung had a spongy appearance and the alveoli were visible grossly. In several cases a bullous emphysema was seen.

On cut section the lung showed a gross dilatation of the entire bronchial tree.



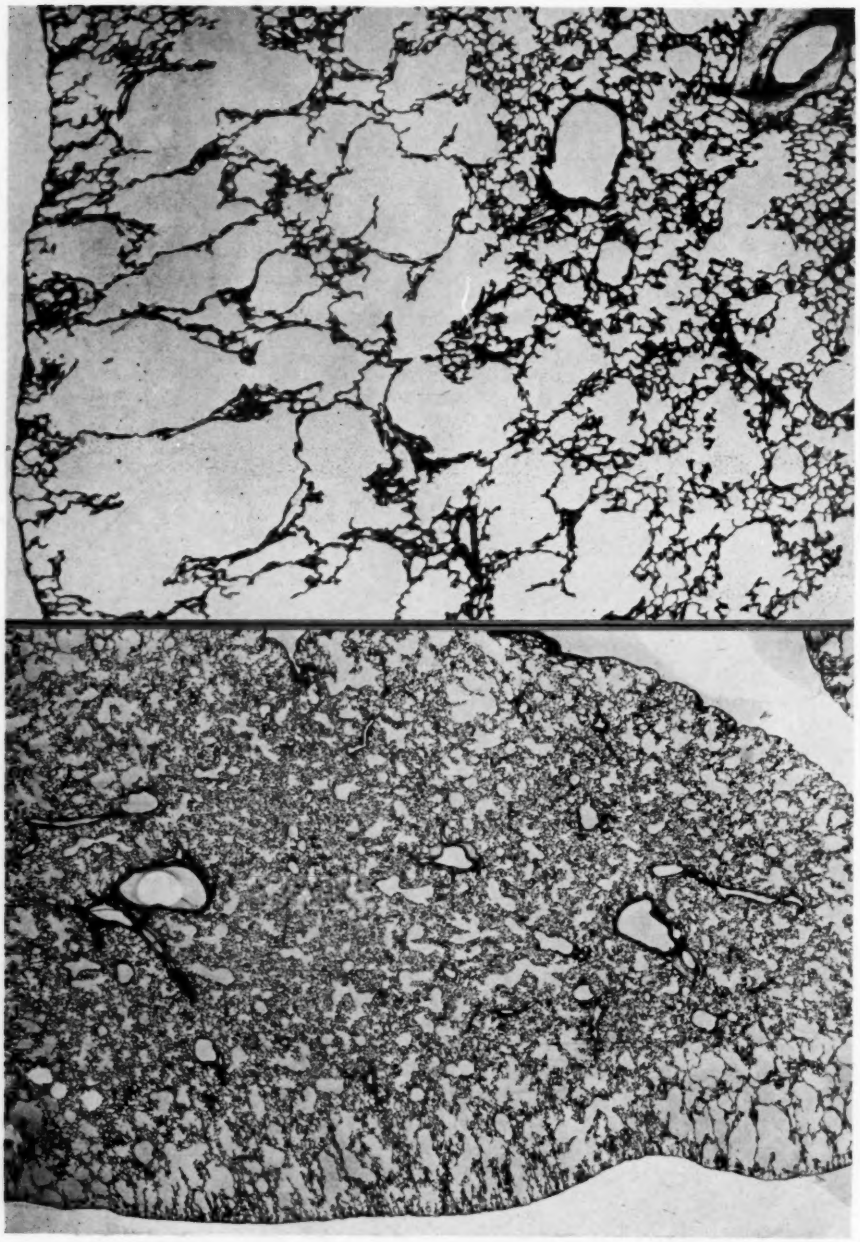
B.

A.

Fig. 6 *A* and *B*.—Dog 917. Bilateral temporary paralysis of diaphragm. Microscopic appearance of aerated lung three months after reduction of lung function to three lobes (38.7 per cent). Note dilatation of terminal respiratory units and similarity to Dog 3 in Fig. 5. (×7 and ×20.)

MICROSCOPIC PATHOLOGY

In general, all sections revealed a dilatation of the air passages. This varied from slight degrees in the larger bronchi to a more extreme degree in the terminal respiratory bronchioles, alveolar ducts and sacs. This dilatation was evident in three-lobe dogs, but we could find little to differentiate animals having permanent paralysis of the diaphragm (Fig. 5 *A* and *B*) from those having the temporary type (Fig. 6 *A* and *B*). Some sections showed diminution in the number of capillaries. The



B.

A.

Fig. 7 *A* and *B*.—Dog 30. Bilateral permanent paralysis of diaphragm. Microscopic appearance of aerated lung one month after final reduction to one lobe (15 per cent). Note peripheral distribution of dilatation of terminal respiratory units. Definite emphysematous change in alveolar ducts and sacs. (×7 and ×20.)

respiratory pores of the alveolar walls were larger, somewhat distorted and more numerous than normal. The elastic and fibrous tissue elements although often somewhat stretched were not found to be disrupted.

The two-lobe group showed similar pathologic changes with possibly slightly more distention of the individual alveoli, with more marked distention of some of the alveolar ducts and sacs.

The one-lobe dogs showed more severe changes, apparently most severe in animals with permanent paralysis of the diaphragm. There was dilatation of the respiratory bronchioles, alveolar ducts and sacs with a breakdown of the alveolar walls under the pleura. The alveolar walls in some areas were thinned into long avascular strands forming large fibrous vesicles (Fig. 7 *A* and *B*). The breakdown was not primarily in the alveoli located immediately beneath the pleura but in the terminal respiratory units, i.e., the alveolar ducts and sacs. Many counts of the alveoli per microscopic field reveal considerable variation among dogs of a group. Averaging all groups one finds the total alveoli per field reduced to approximately one-half the normal.

We are of the opinion that this marked dilatation of the terminal air passages does not represent true emphysema as some authors believe, since the capillary, elastic, and connective tissue fibers are intact.

The walls of the alveolar duct between the alveolar sacs and alveoli are made up of muscle cells, elastic and collagenous fibers.[9] In their sections these appear as short knobs or clubs running parallel to the long axis of the duct. These have been described erroneously as pathologic "clubbings."*

CLINICAL APPLICATION

Within the last decade marked improvement has been effected in the management of intrathoracic operations. This has been especially noticeable in the resection of lung tissue for neoplastic and inflammatory diseases. Whereas lobectomy for bronchiectasis was once fraught with grave danger, now it is accomplished with relatively little risk. Total pneumonectomy, unsuccessful prior to Graham's[10] first case in 1933, although an operation less safe than lobectomy, is being successfully performed in increasing numbers.

Very frequently, however, the distribution of the lesion in bronchiectasis, includes more than one lobe on one or both sides of the chest. The problem confronting the surgeon has been not only whether the general condition of the patient warranted operation, but how much lung tissue could be safely resected and which side should be resected first. Another disputed point concerns the resultant pleural space. Should the diaphragm be paralyzed temporarily or permanently, if at all, in order to obliterate better the space formerly occupied by the resected lung tissue? Also what effect if any would diaphragmatic paralysis

*We wish to express our appreciation to Dr. Clayton G. Loosli for his criticism and instruction concerning the microscopic changes of the lungs.

exert on the compensatory changes developing as a result of overdistention of the remaining functioning lung? Another much debated question is whether a thoracoplasty should accompany or follow total pneumonectomy. This latter also applies to the immediate postoperative course as well as to the effect on the resultant alteration in cardiorespiratory function due to overdistention and resultant compensatory alteration of the remaining functioning lung.

Resection of Lung Tissue.—The above-described experiments demonstrate that a large part of the lung may be removed with safety, without materially influencing the cardiorespiratory function. When tested by exercise or by reduced atmospheric pressure, the respiratory reserve of dogs with three lung lobes (38.7 per cent) remaining, compared favorably with that of normal animals, while the reserve of one-lobe dogs (15 per cent) was only slightly lowered.

The interval between operations and especially the general condition at the time of the operation were of definite significance. Suffice it to say that sufficient time should elapse between stages to insure adequate return of general resistance with little evidence of toxic manifestation remaining. This period may vary from six weeks to six months.

Another factor of importance was the amount of lung resected at each operation. The above results would indicate that the side of greatest involvement should be resected first, lesser amounts of lung tissue being removed at the second operation.

Diaphragmatic Paralysis.—Obliteration of the residual pleural space following lobectomy or bilobectomy may be more easily accomplished by paralyzing the diaphragm. When obliteration is complete and maintained within twenty-four hours after operation, primary healing is encouraged and the convalescence made smoother. A temporary type of paralysis is the more advisable since it has all the advantages of the permanent type immediately after operation and function may be expected to return within two months or by the time the second operation is made. The temporary type is also desirable from the standpoint of compensatory overinflation of the remaining lung. This change is thus more evenly distributed and not as exaggerated at the periphery of the lung. In this regard, however, compensatory overdistention appeared not to influence greatly the function of the lung tissue since one-lung (15 per cent functioning) dogs with or without bilateral diaphragmatic paralysis exhibited no dyspnea or cyanosis while at rest and tolerated reduction of atmospheric pressure equally well and almost within normal limits. On exercise they were mildly dyspneic.

SUMMARY

1. Bilateral resection of as much as 62 per cent of the total lung tissue within a period of three weeks was well tolerated in normal dogs, when no complications occurred after the first operation. Sufficient

respiratory reserve remained following further reduction to 15 per cent so that the animals were able to tolerate moderate exercise and reduction of atmospheric pressure to almost the limit of normal dogs (25 to 30,000 feet).

2. Bilateral temporary or permanent paralysis of the diaphragm was well tolerated whether the lung function was one lobe or three lobes. Compensatory alterations of the lung from overdistention were of about the same degree in temporary or permanent paralysis but different in distribution. In permanent paralysis these changes were more peripheral and there was more tendency to bullae formation. In the temporary type the alterations were more evenly distributed.

3. In the absence of complications following the above procedures, the animals remained in a healthy state for the duration of the experiments; that is, six to twelve months.

4. From the above findings it would appear that temporary paralysis of the diaphragm is a justifiable procedure in the human being. In bilateral operations it seems advisable that sufficient time elapse between stages for re-establishment of the diaphragmatic function and improvement of the patient's general health.

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THE EFFECT OF REPLACEMENT THERAPY IN EXPERIMENTAL SHOCK

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IT HAS been known for many years that a reduction of the effective blood volume is an essential feature of shock regardless of cause. Recently considerable attention has been directed to the pathologic changes which occur in the tissues in shock. These consist principally of marked diffuse congestion of capillaries and venules in visceral areas, especially the lungs, liver, kidneys, and gastrointestinal tract. The relation of these pathologic changes to the reduced blood volume and the significance of this relationship in the treatment of experimental shock due to severe thermal trauma constitute the subject of this paper.

In a previous study[1] the contention of Blalock[2] that the principal reduction of the blood volume in early traumatic shock is due to a loss of fluid at the site of injury was confirmed. Anesthetized animals were subjected to severe thermal and mechanical trauma and the changes in the pulse, blood pressure, hematocrit, plasma and total blood volumes recorded. As shown in Fig. 1 immediately following such an injury there was a rapid reduction of the blood volume. Within three hours there was marked hemoconcentration and the plasma volume was reduced to approximately two-thirds of its original total. The blood pressure after an initial fall rose to above so-called shock levels and was well sustained until late in the experimental period. A falling blood pressure usually was indicative of impending collapse and death. Pathologic examination of animals sacrificed in the early stages of shock disclosed no evidence of loss of fluid into tissues other than at the site of injury. There were no significant pathologic changes in the viscera. However, when animals were allowed to die in shock or when the experiments were terminated in the late stages after the blood pressure had fallen, pathologic examination disclosed congestion and dilatation of capillaries, capillary hemorrhages, edema and in some instances, particularly in the liver, degenerative changes in parenchymatous tissues. It was concluded that under the conditions of these experiments the principal reduction of the blood volume was due to a loss of fluid at the site of injury and that the pathologic changes in the viscera were a secondary rather than a primary phenomenon.

The present study was designed to correlate the physiologic effects of fluid replacement with the pathologic changes in shock. Are these

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

tissue changes a consequence of the reduced blood volume or are they due to some factor, such as a toxin absorbed from the site of injury which produces generalized capillary injury irrespective of the level of the blood volume? If the pathologic changes are a consequence of the lowered blood volume, it should be possible to prevent them by restoring the blood volume to normal. This has been attempted both in the early and late stages of experimental shock due to thermal trauma.

The experimental procedure and methods used were the same as has been described in detail previously.[1] Large mongrel dogs were used in all the experiments. Shock was induced by thermal trauma. Determinations of the pulse, blood pressure, hematocrit, plasma volume, hemoglobin, and serum proteins were made before and at varying intervals after the injury. The experiments were divided into three groups. In

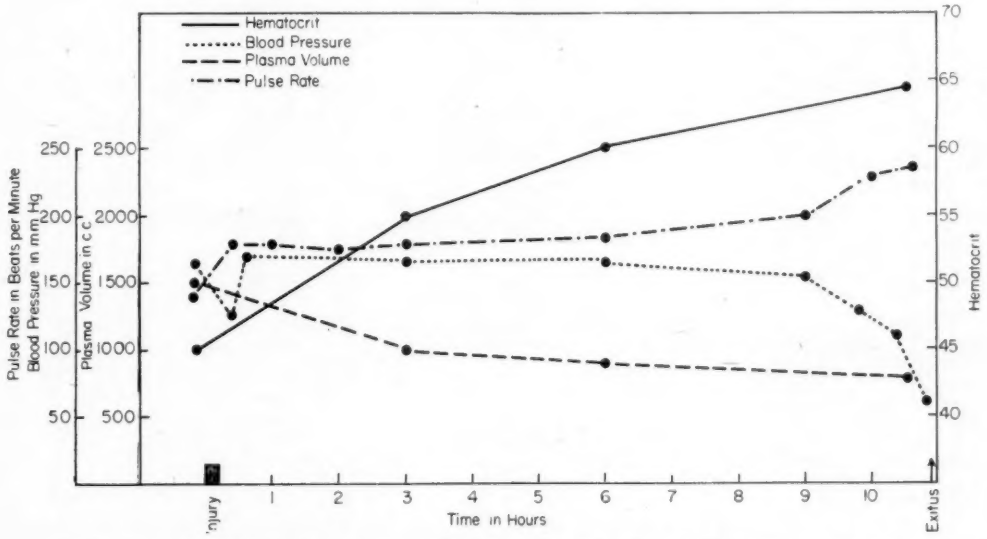

Fig. 1.—The typical course of the changes in hematocrit, blood pressure and plasma volume in experimental shock due to thermal trauma.

one the effects of treatment in late shock were observed. In another the response and end results of a single infusion of plasma or saline solution in early shock were determined and finally, the effects of continuous infusions of plasma were studied. The results are tabulated in Table I. Individual experiments representative of each group are shown in the accompanying graphs.

TREATMENT IN LATE SHOCK

The inefficacy of treatment in late shock is well known. It has been thought that at this stage fluid leaked out of the vascular system through damaged capillaries so rapidly that the blood volume could not be restored to normal. That this is not the case is shown in Experiments 1, 2, and 3 (Table I). In these experiments therapy was instituted after the blood pressure had fallen, indicating an advanced degree of shock.

TABLE I

EXPERIMENT	WT. (KG.)	TYPE OF THERAPY	TIME (HR.)	PULSE	SYSTOLIC BLOOD PRESSURE	HEMATOCRIT (VOL. %)	PLASMA VOLUME (C.C.)	HB. (GM. %)	SERUM PROTEIN (GM. %)	COURSE OF SHOCK	PATHOLOGY
1	22.2	Whole blood 200 c.c.	Before injury	130	140	40.5	945	14.5	5.5	Blood volume increased but no systemic improvement. Blood pressure continued to fall. Animal died.	Usual late tissue changes
			7 hr. after injury	205	90	64.1	563	21.0	6.9		
			1 hr. after treatment (8 hr. after injury)	230	60	64.6	692	21.0	6.9		
2	27.1	Whole blood 200 c.c.	Before injury	100	130	48.9	1,130	15.6	5.2	Volume increased without improvement of general condition. Animal died.	Usual late tissue changes
			8 hr. after injury	240	110	59.0	563	18.5	7.7		
			1 hr. after treatment (8½ hr. after injury)	260	60	57.7	715	17.2	7.4		
3	23.1	Plasma 200 c.c.	Before injury	140	110	51.3	886			Despite marked increase of plasma volume there was no improvement. Death occurred with the plasma volume above the normal level. Animal died.	Usual late tissue changes
			7½ hr. after injury	210	70	56.5	753				
			1½ hr. after treatment (9¼ hr. after injury)	280	40	49.6	993				
4	22.5	Saline solution 1,000 c.c.	Before injury	180	130	47.0	1,040	15.1	6.0	Blood volume raised only slightly by saline infusion. Marked dilution of serum protein. Animal sacrificed.	Marked tissue changes, especially edema
			4 hr. after injury	240	140	56.5	700	17.7	5.9		
			½ hr. after treatment (6 hr. after injury)	220	120	41.6	676	13.4	4.9		
			2 hr. after treatment (8 hr. after injury)	240	100	54.7	625	20.0	3.5		
5	24.8	Saline and bicarbonate solution 310 c.c.	Before injury	140	140	48.1	1,065	17.7	7.0	Only temporary improvement from infusion accompanied by marked dilution of serum protein. Animal sacrificed.	Very marked tissue changes, especially edema, for this duration of shock
			3¾ hr. after injury	175	140	68.0	578	24.3	6.2		
			¼ hr. after treatment (4¼ hr. after injury)	150	130	48.5	1,174		4.5		
			2½ hr. after treatment (6¾ hr. after injury)	200	130	63.5	760	27.3	5.3		

6	17.4	Plasma 200 c.c.	Before injury	130	160	48.3	762	16.5	5.9	Marked improvement with plasma but this was not maintained. No dilution of serum protein. Animal sacrificed.	No striking alteration of the usual tissue changes
			4¼ hr. after injury	180	140	65.8	561	20.0	6.8		
			¼ hr. after treatment (4½ hr. after injury)	150	150	53.0	780	17.8	7.7		
									6.4		
			2¾ hr. after treatment (7 hr. after injury)	210	150	58.0	600	19.7			
7	21.3	Plasma 200 c.c. 1 hr. after injury	Before injury	128	130	43.1	1,335	14.1	6.9	Single infusion inadequate to maintain plasma volume.	No striking alteration of the usual tissue changes
			½ hr. after injury	130	130	52.0					
			1 hr. after treatment (3 hr. after injury)	150	140	57.2	900	19.0	6.8		
									6.8		
			5 hr. after treatment (6 hr. after injury)	160	130	55.5	865				
8	21.4	Plasma 400 c.c. Saline solution 500 c.c. Continuous infusion of plasma started ½ hr. after injury (see Fig. 6)	Before injury	150	140	51.7	872		6.3	Marked dilution of serum protein after saline solution.	Considerable amelioration of usual late tissue changes (see text for discussion)
			4 hr. after plasma (5 hr. after injury)	150	140	46.9	945		5.4		
			6½ hr. after injury (½ hr. after saline)	160	150	39.8			4.3		
			8 hr. after injury	190	150	51.5	775				
9	18.8	950 c.c. Plasma (protein 2.5 Gm. per cent). Continuous infusion begun 1 hr. after injury (see Fig. 7)	Before injury	160	160	54.2	802		6.3	Slight fall in plasma volume but general condition of animal well sustained. Replacement not quite adequate.	Marked amelioration of tissue changes (see text for details)
			½ hr. after injury	150	140	59.0	710		6.3		
			6 hr. after injury								
			8¾ hr. after injury	140	140	54.2	638		6.5		
10	21.3	700 c.c. Plasma (protein 5.5 Gm. per cent). Continuous infusion begun 2 hr. after injury	Before injury	150	140	45.5	1,370		6.5	Blood volume increased by infusion. No hemoconcentration.	Marked amelioration of tissue changes (see text for details)
			½ hr. after injury	160	140	39.6			6.3		
			6 hr. after injury	150	140	38.8					
			9 hr. after injury	140	140	36.3	1,696		6.3		

The response to a transfusion of whole blood is shown in Fig. 2. Although there was a considerable rise in the blood volume the blood pressure continued to fall and exitus occurred with the blood volume at a nearly normal level. Note that there was no improvement in the hemoconcentration. A somewhat similar response occurred when plasma was used (Fig. 3). Here, however, there was a temporary rise in the blood pressure and considerable improvement of the hemoconcentra-

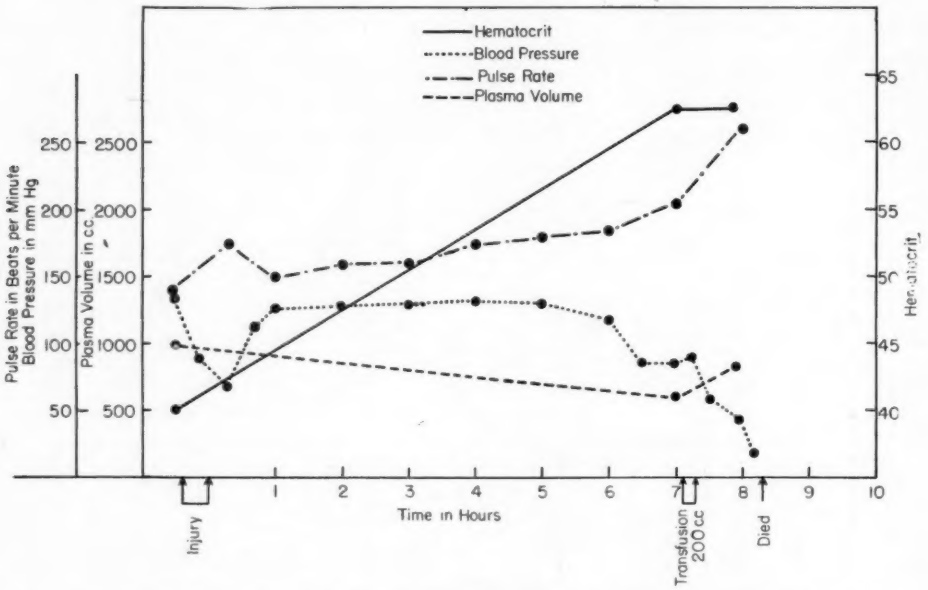

Fig. 2.—The effect of a transfusion of blood in the late stage of experimental shock.

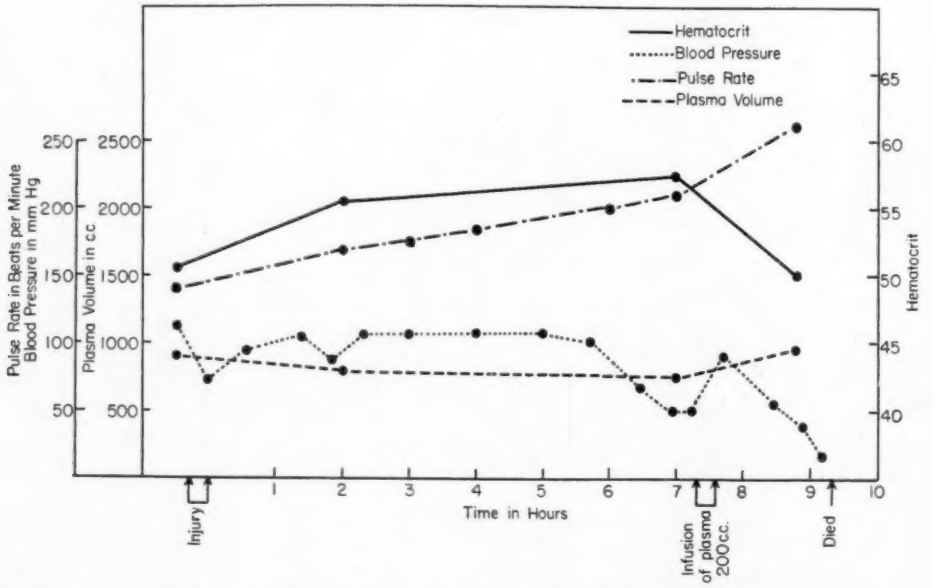

Fig. 3.—The effect of an infusion of plasma in the late stage of experimental shock.

tion. However, death occurred when the plasma volume was normal. Post-mortem examination in Experiments 1, 2, and 3 revealed the usual gross and microscopic changes of late shock. These have been described in detail elsewhere[1] and will not be elaborated on here. Suffice it to say that no alteration of the usual tissue changes which follow prolonged anoxia could be demonstrated. It is concluded that therapy instituted in the very late stages of shock has no demonstrable effect on the pathologic changes in the tissues and even though it restores the blood volume to normal the course of the shock is not greatly altered. Under these circumstances death may occur with a normal plasma volume (Experiment 3). This suggests that once well established the pathologic changes in the tissues are irreversible and therapy, to be effective, must be instituted before such generalized tissue injury occurs.

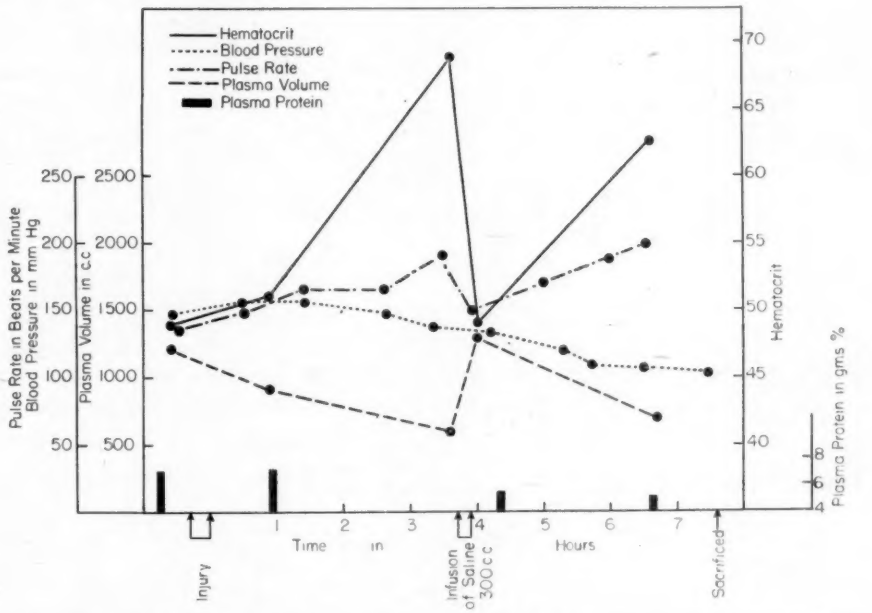

Fig. 4.—The effect of an infusion of saline and bicarbonate solution in experimental shock.

TREATMENT IN EARLY SHOCK

In Experiments 4, 5, 6, and 7 therapy was started shortly after the plasma volume had fallen. An amount of fluid calculated to restore the volume to normal was given. The comparative efficacy in this respect of a noncolloidal solution and plasma is shown in Figs. 4 and 5. When saline solution was given, there was a marked improvement in the hemoconcentration and a rise in the plasma volume. However, this was accompanied by such a dilution of the blood that the concentration of serum proteins fell to edema levels. The danger of using saline solutions in shock has been emphasized before. Beard and Blalock[4, 5] observed that animals which received saline infusions often seemed worse

after the infusion was stopped than if no therapy had been given. This was confirmed in the present study. Moreover, it was found that the pathologic changes in the tissues, particularly edema, seemed more striking following saline infusion than when no therapy was given (Experiments 4 and 5).

The superiority of plasma as a replacement fluid in shock has been demonstrated by a number of investigators.[6-8] Considerable emphasis has been placed on the idea that there is no dilution of the serum proteins, that the osmotic pressure of the blood is not lowered, and that, therefore, the improvement following its use is more permanent than when saline or dextrose solutions are given. It should be emphasized

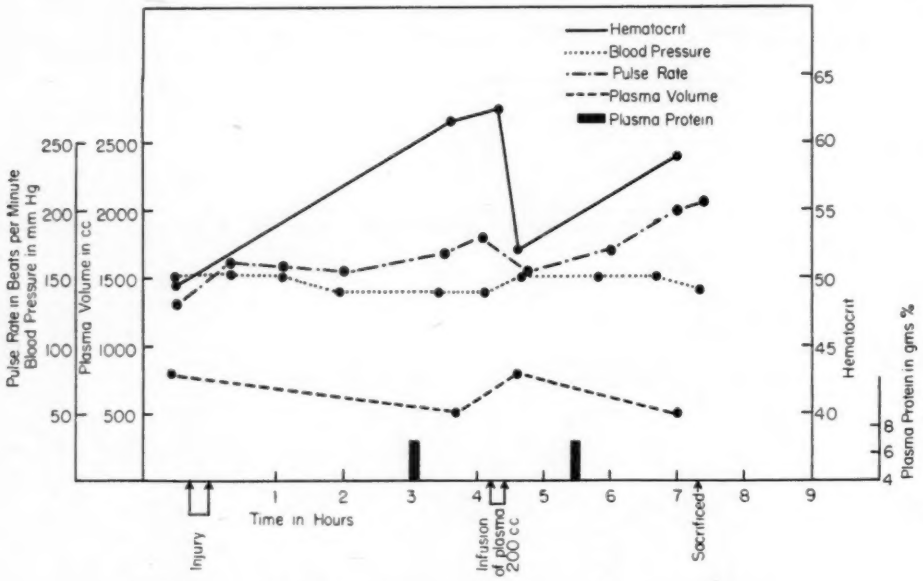

Fig. 5.—The effect of an infusion of plasma in experimental shock.

that although the beneficial effects of plasma are considerable, the duration of the improvement following its use in severe thermal trauma was of short duration (Experiments 6 and 7) (Fig. 5). With the important exception that there was no dilution of the plasma proteins, the affect on the blood volume of a single infusion of plasma in severe shock was little different than when saline solution was used. This does not mean that plasma is not greatly superior to saline solution, but it serves to emphasize that repeated infusions of plasma are often necessary. Moreover, on pathologic examination there was no striking change in the appearances of the tissues in animals which received only a single infusion of plasma.

In the final group of experiments[8, 9, 10] therapy was instituted early and maintained throughout the experimental period. In Fig. 6 is shown the response to a 400 c.c. infusion of plasma followed by a 500 c.c. infusion of saline solution. Five hours after the injury there was no

hemoconcentration and both the plasma and total blood volumes were normal. The concentration of serum proteins was normal. However, immediately after the infusion of saline solution there was a fall in the hematocrit to subnormal levels and a dilution of the serum proteins. Two hours later the plasma volume was considerably reduced. At post mortem pathologic changes in the viscera were found, but these were less marked than are usually found in experiments of this duration. There was considerable edema of the lungs, but the gastrointestinal tract showed but little variation from the normal. The loss of protein in this experiment merits comment. The infusion of plasma at the rate of 100 c.c. an hour sufficed to maintain the total protein of

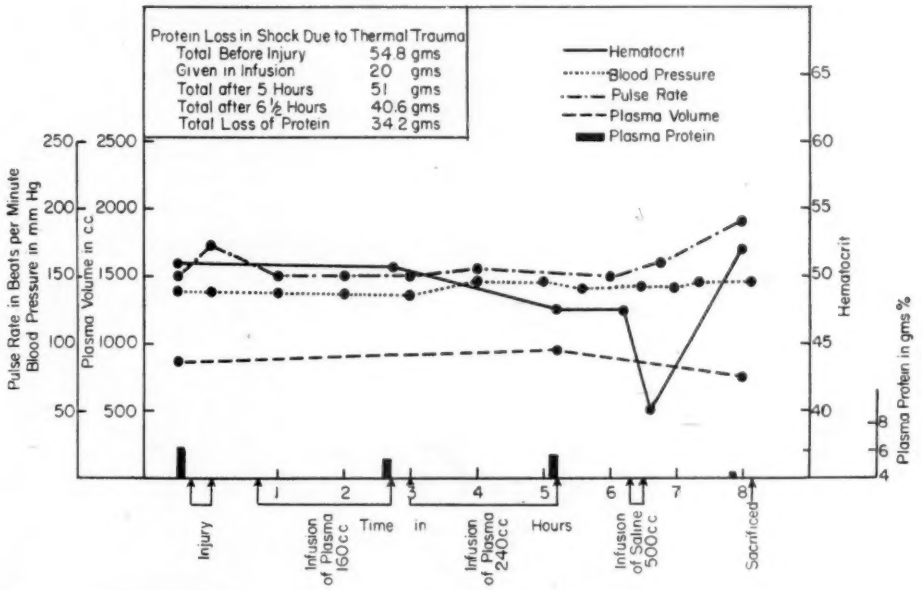

Fig. 6.—The effect of plasma infusion followed by saline infusion in experimental shock.

the body at normal levels for four hours. Despite this amount of replacement, immediately after saline solution was used there was a fall in the total amount of protein as well as a considerable reduction of the concentration of proteins. This, again, serves to demonstrate the dangers of saline solution in shock of this type even when it is used as an adjunct to plasma.

The effects of continuous infusions of plasma were studied in Experiments 9 and 10. In one of these (Fig. 7) an infusion of 950 c.c. of plasma (protein content 2.5 Gm. per cent) was given over a period of seven and one-half hours. This was sufficient to maintain the plasma volume at nearly normal levels throughout the experiment, but there was a progressive dilution of the plasma proteins indicating that the replacement was not quite adequate. In Experiment 10, 700 c.c. of plasma (protein content 5.5 per cent) was given over a period of eight hours.

Not only was this sufficient to maintain the level of the plasma protein but actually it brought about an increase in the plasma volume (Table I). It would appear that to a certain extent the earlier and more adequate the replacement therapy, the less fluid is required and the less extensive is the protein loss. If treatment is delayed until the blood volume has fallen, generalized capillary damage occurs and the possible areas from which fluid may escape are greatly increased. Moreover, if the protein composition of the replacement fluid is greatly lower than that of plasma, this fluid may escape from the blood stream with a higher protein content than when it entered, thereby increasing the rate of protein loss.[4, 5]

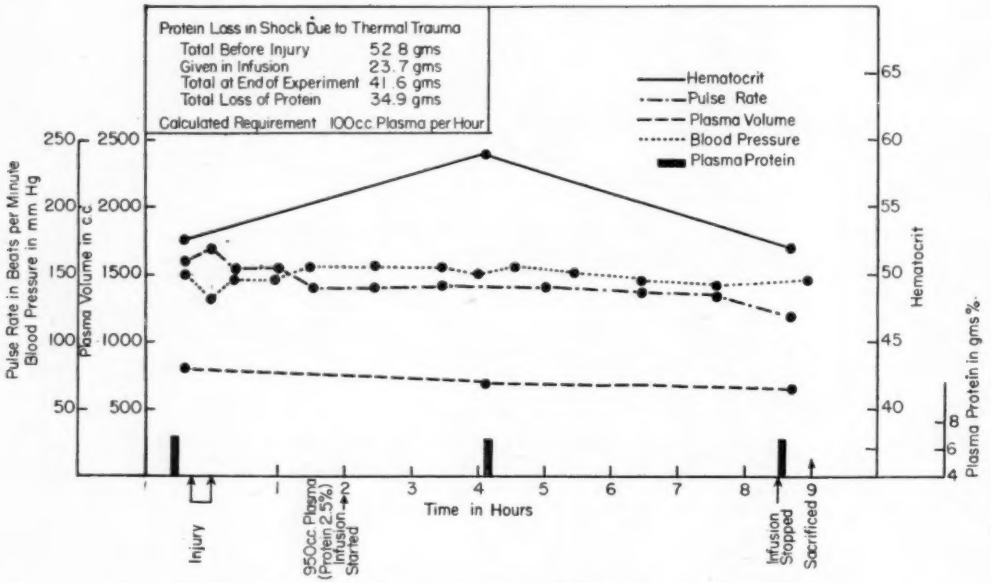

Fig. 7.—The effect of a continuous infusion of plasma in experimental shock.

Pathologic examination in Experiments 9 and 10 disclosed very marked amelioration of the usual late tissue changes. Grossly there was no obvious variation from the normal except for slight atelectasis and congestion of the dependent portions of the lower lobes of both lungs and moderate congestion of the kidneys. The entire gastrointestinal tract, liver, pancreas, and adrenals appeared normal. On microscopic examination there was minimal evidence of capillary dilatation in the lungs, kidneys, and adrenals. These changes have been described before as occurring even in the early stages of shock, under the condition of these experiments, and probably are due to the use of sodium pentobarbital as the anesthetic. However, the usual marked tissue changes of advanced shock were not present. The liver showed no congestion of the sinusoids or degenerative changes in the cord cells, although in some areas there were collections of polymorphonuclear

leucocytes scattered through the sinusoids. No evidence of edema, congestion, or capillary injury was found in the gastrointestinal tract on microscopic examination. Thus, although it cannot be said that following adequate replacement therapy there is no evidence of generalized capillary injury, there is such a striking amelioration of the usual pathologic changes as to lead us to believe that these are principally the result of anoxia, secondary to the reduction of the blood volume and hence are largely preventable by early and adequate therapy.

The amount of protein necessary to maintain an adequate level in severe shock requires further comment. As shown in Figs. 6 and 7, the total loss of protein in eight to nine hours of severe shock may amount to as much as 35 Gm. If given as plasma in a concentration of 5 Gm. per cent, it would take roughly 80 c.c. of plasma per hour to maintain a normal level, assuming that treatment was started shortly after injury. However, as shown in Fig. 1, the principal reduction of the plasma volume occurs within the first few hours of injury so that if treatment were delayed even for two or three hours, the rate of replacement would necessarily have to be higher to make up the deficit. In the experimental animal with a blood volume of 2.5 liters approximately 75 to 100 c.c. of plasma per hour would seem necessary (Experiments 8, 9, and 10). If we transpose this estimate to the clinic, it means that a severely burned patient weighing 70 kg. would require between 100 to 200 c.c. of plasma per hour for the first ten hours after injury. Although this figure is considerably in excess of the amounts usually used, in a recent clinical study Elman[9] suggested that as much as 1,400 c.c. may be required. It seems likely that the sudden, unexplained collapse of patients in the early stages of severe burns may be due to this enormous reduction of the plasma volume.

How long therapy must be maintained has not been determined in this study. It is hardly practical to do so in the laboratory because of the complicating factor of prolonged anesthesia. On the basis of a recent clinical study[10] it has been suggested that plasma loss may continue for as long as forty hours.

SUMMARY

Under the conditions of these experiments, replacement therapy instituted in the late stages of experimental shock has no effect on the pathologic changes in the tissues even though it restores the blood volume to normal. In early shock a single infusion of saline solution, in amount calculated to raise the blood volume to normal, not only is of temporary benefit but causes such a dilution of the plasma proteins that the late tissue changes of shock are accentuated. Under the same circumstances the beneficial effects of a single infusion of plasma are also of only short duration and bring about no alteration of the pathologic

changes. By a continuous infusion of plasma, begun early in the experimental period, the blood volume may be maintained at normal levels and under such circumstances there is a marked amelioration of the late tissue changes in shock. The amounts of plasma necessary to do this are considerably in excess of those generally used in the treatment of burns in patients.

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REACTIONS TO LOCAL ANESTHETIC AGENTS

I. Experimental Studies With Procaine

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ALTHOUGH local anesthesia has proved through long use to be a very valuable aid in surgery, in many instances the anesthesia of choice and undoubtedly the safest of all methods of rendering surgery painless, alarming and even fatal reactions sometimes occur. Efforts have been made toward an understanding of these reactions, and suggestions relating to their prevention and treatment have been offered; and yet many problems remain unsolved.

This communication reports some efforts to elucidate a few of these problems. I have been interested in trying to learn something concerning the cause of death, the difference between the "collapse" and the "respiratory failure-convulsive" types of reaction, the influence of the route of administration, the concentration of the injected solution, and the age of the subject upon the toxicity of procaine, the use of local anesthesia during general ether anesthesia, and possible prophylactic and therapeutic aids.

Much is known from experimental and clinical studies concerning the relative merits and inherent dangers of the various members of the group of cocainelike anesthetics, and it is generally agreed that procaine is the safest and most useful agent for local infiltration or nerve blocking.[1-5] It is also known that although these drugs differ from one another in relative toxicity, the reactions they may evoke are essentially alike. For these reasons and because procaine is the most widely used of these agents, these experiments have been limited to a study of this one drug.

MATERIALS AND METHODS

Each day a fresh solution was prepared from U.S.P. procaine crystals and distilled water. A 10 per cent solution was used throughout except in the study dealing with the effect of concentration, in which 1 per cent and 0.5 per cent solutions were also used. The dosage of procaine was on a basis of body weight in kilograms. All intravenous injections were made as rapidly as possible. In the paravertebral injections the solution was colored with a minute amount of gentian violet so that the accuracy of the injection could be determined at autopsy. The procaine to which the gentian violet had been added underwent a slight diminution in toxicity as determined by bio-assay with intravenous injections.

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

A correction for this was accordingly made. Normal healthy guinea pigs and mongrel dogs were used. That group of guinea pigs which are described as "young" were actively growing animals varying in weight from 300 to 450 Gm. (average 389 Gm.); those described as "old" were one year older than the first group and varied in weight from 500 to 640 Gm. (average 575 Gm.).

Mean arterial blood pressure was measured by a kymographic recording mercury manometer connected with a cannula in the common carotid artery, a small bulb near the cannula filled with citrate solution being used to prevent clotting. Oxygen consumption as well as respiratory rate and minute volume were measured by means of a Sanborn motorgrafic metabolism tester attached to a tracheal cannula. Blood samples were collected from the carotid artery and placed in flasks containing dried potassium and ammonium oxalate.* This method prevents clotting without causing shrinkage of the erythrocytes. Wintrobe hematocrit tubes were used; proteins were estimated by the falling drop method with the La Motte densimeter; plasma volume was determined with the photoelectric microcolorimetric technique with the azo-blue dye T1824.[6] At least three injections of dye were made in each instance in order to determine accurately the rate of disappearance of the dye. Blood procaine estimations, free and total, were made according to a modification of Bratton and Marshall's[7] method for determination of sulfanilamide, which permitted accurate assay of 0.2 c.c. of blood. Concentration was determined from photoelectric colorimetric readings, a standard curve having been established with procaine solutions of known strength.

EXPERIMENTAL OBSERVATIONS AND COMMENTS

When guinea pigs are given a lethal dose or more of procaine subcutaneously, intramuscularly, or by any route where slow absorption presumably takes place, the sequence of events is ordinarily fairly uniform. After an interval of some minutes the animal becomes "groggy," and shortly afterward falls over with diminution or loss of consciousness. Irritative central nervous system phenomena ensue, at first muscular twitchings and purposeless movements and rapidly thereafter generalized convulsions. During this period respirations are ordinarily increased. After a time the convulsions become weaker and the heart stops and respirations cease. Generally but not invariably the last respiratory gasp precedes by a moment or so cessation of the heart beat. Sometimes weak respirations continue momentarily after the heart beat is no longer perceptible. In general, one is impressed by the fact that cardiac and respiratory failure occur almost simultaneously. Occasionally on the approach of death a little froth is seen at the nostrils.

*One and three-tenths grams of ammonium oxalate and 0.7 Gm. of potassium oxalate in 100 c.c., 0.1 c.c. for each cubic centimeter of blood (Wintrobe).

If a fatal dose is given intravenously, the animal almost immediately falls over as if unconscious, convulsions begin, respirations cease or are replaced by infrequent gasps, and the heart beat rapidly becomes imperceptible. Heart beat and respirations often stop simultaneously. Frequently a weak respiration or two follow cessation of the heart beat as determined by palpation of the chest. Sometimes the reverse is true, and in every instance in which the thorax was opened immediately after cessation of respiration and loss of heart action as determined by palpation, the heart was found to be beating weakly. Whenever death followed an intravenous procaine injection in an animal previously given nembutal or ether, respirations always ceased before the heart beat was no longer palpable. At autopsy, regardless of the route of administration of the procaine, no gross pathologic change was noted. The lungs did not appear edematous.

It was thought advisable to follow graphically certain changes in larger animals. The experiment was as follows: A dog was placed upon the operating table, and with 10 per cent phenol as a local anesthetic, the trachea and one common carotid artery were cannulated. Blood pressure was recorded continuously on a kymograph and pulse and respiratory rates were charted at intervals. Intermittent graphic records of respiratory rate and volume as well as oxygen consumption were made by attaching the tracheal cannula to the metabolism machine. Samples of blood were drawn at intervals for hematocrit, protein, and plasma volume estimations. After a suitable period of normal control observations, procaine was administered. Several experiments are illustrated in Figs. 1, 2, and 3.

In the experiment recorded in Fig. 1, 1,000 mg. of procaine per kilogram of body weight was given subcutaneously; in that recorded in Fig. 2, 700 mg. per kilogram was given subcutaneously at the beginning and the same dose toward the end of the experiment. During the control period there were minor fluctuations in blood pressure, hematocrit, plasma proteins, and plasma volume, greater fluctuations in pulse, and still greater in respiratory rate and minute volume. These variations must be taken into consideration in analyzing the data obtained during the procaine reaction. In these experiments one is impressed by the relative constancy of hematocrit, plasma proteins, and plasma volume. No significant change is noted. It will be observed that the blood pressure tends to rise slightly or moderately after the procaine is administered and to be well maintained until the terminal period of collapse begins, when it drops precipitously to zero accompanied by a sudden cessation of heart beat and respirations. In general, the respiratory rate tends to rise during the reaction, as does the minute respiratory volume, until near the end it suddenly becomes slow and respirations cease. No characteristic change in oxygen consumption is

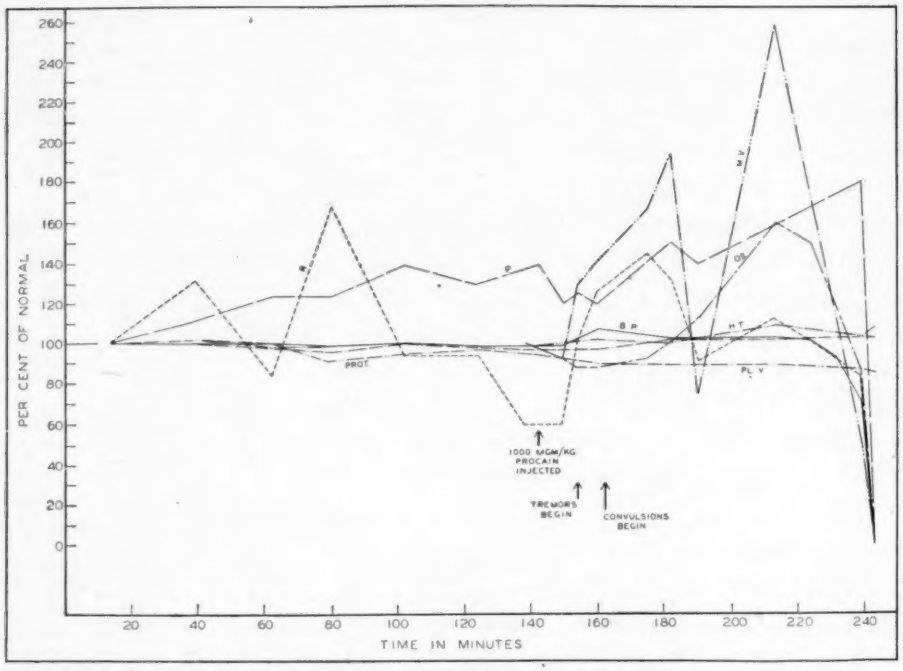

Fig. 1.—Chart showing changes in hematocrit, plasma proteins, plasma volume pulse, blood pressure, respirations, minute volume, and oxygen consumption in a dog during a fatal reaction from procaine injected subcutaneously.

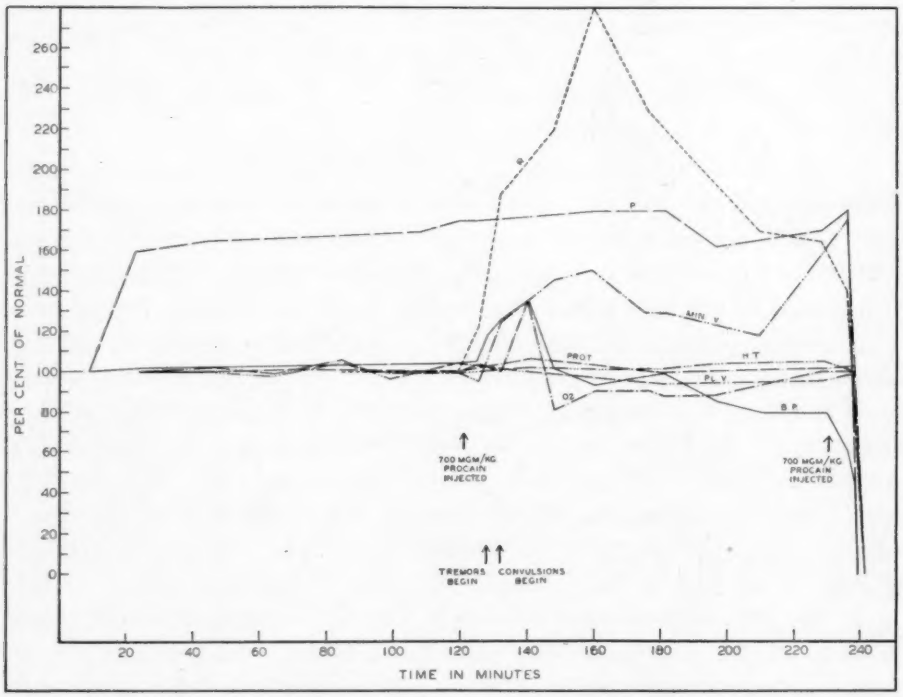

Fig. 2.—Same as Fig. 1. The procaine was injected subcutaneously in two doses.

noted; the increases which occurred seemed related to convulsive movements and restlessness. It will be noted that in the first experiment heart beat and respirations ceased simultaneously and that in the second experiment a few weak respirations persisted for two minutes after pulse and heart beat were no longer perceptible.

In Fig. 3 is recorded an experiment in which increasingly large intravenous doses of procaine were given at intervals. It will be seen that a transient rise in blood pressure follows a very small dose of procaine. After a somewhat larger dose a momentary fall in blood pressure is rapidly succeeded by a rise to a higher than normal level. When a nearly lethal dose is injected, the drop in pressure is continued a little longer; and finally, when a lethal dose is injected a precipitous drop to

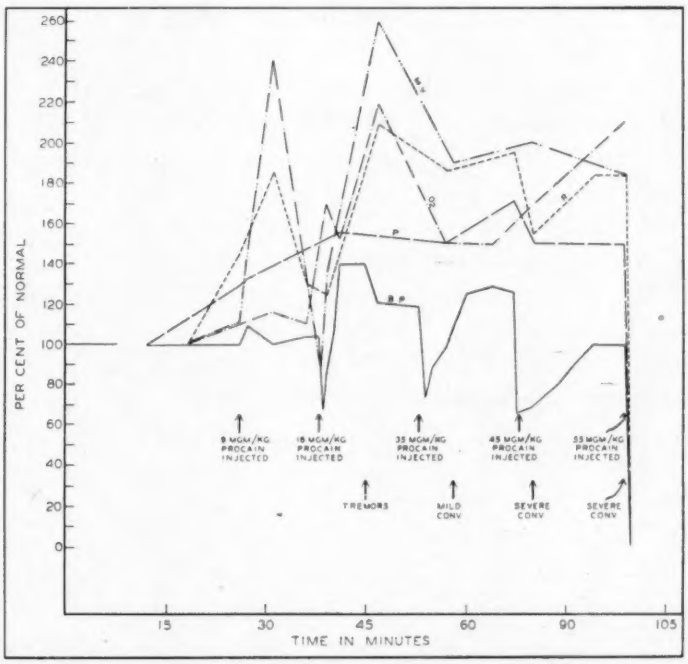

Fig. 3.—Chart showing changes in blood pressure, pulse, respiratory rate, minute volume, and oxygen consumption in a dog given gradually increasing intravenous doses of procaine.

zero occurs simultaneously with cessation of respirations. Except for the transient drop in pressure following injection of moderate doses of procaine, the blood pressure trend is much like that observed after subcutaneous injection of procaine. Pulse, respirations, minute volume, and oxygen consumption behaved much as in the preceding experiments.

From these observations one may say that the terminal circulatory collapse is not the result of any loss of plasma volume. It seems unlikely that death is consequent on any peripheral action of the drug. The abrupt and almost simultaneous cardiac and respiratory failure suggests rather that death ensues from central medullary paralysis, although this is not definitely proved.

Clinically two types of severe reaction to toxic doses of local anesthetics are observed. Briefly, in one, death is sudden and is characterized by abrupt circulatory collapse, and in some instances heart beat and respirations cease almost instantaneously. There may or may not be convulsions. The other reaction is more prolonged and is characterized by convulsive manifestations and finally respiratory and cardiac failure. The latter type has been often reproduced experimentally by subcutaneous injection of a fatal dose of procaine and the rapid death following intravenous administration of a lethal dose in experimental animals has been assumed to represent the collapse type of reaction.[8, 9] It has been suggested, therefore, that the one is dependent upon slow absorption of a toxic dose and the other upon rapid absorption of a toxic dose.

Although Hatcher and Eggleston[10] had found that heart beat and respirations ceased together after intravenous administration of novocaine in cats, Knoefel and his co-workers[8] suggested, from kymographic records of blood pressure and respirations following intravenous injections of cocaine in dogs, that death from intravenous injections is due to direct paralysis of the heart. It is interesting that the kymographic tracing which they have used to illustrate this point shows that respirations are stimulated immediately, even before the blood pressure has begun to fall, and that they cease altogether within forty-five seconds of the time the pressure has dropped to a critically low level, and within sixty seconds of the completion of the injection of cocaine. They felt that death after subcutaneous injections, on the other hand, was primarily a respiratory one. It has been generally assumed that the convulsive manifestations of these reactions are due to action of the drug on the brain and that respiratory failure is due to central medullary paralysis. In the early cocaine experiments of von Anrep[11] it was concluded that the changes in blood pressure were due to action of the drug on the vasomotor center, that the initial acceleration of the heart rate was due to the elevated blood pressure and to vagal paresis, and that death was due to respiratory failure.

My experiments confirm the general belief that the "collapse" type of reaction is more nearly reproduced by rapid absorption or by direct intravenous injection of procaine and the other type by slow absorption from subcutaneous or other tissues. As regards a different mechanism of death in the two instances, however, one would suppose a priori that regardless of the mode of injection or the site of lethal action, procaine must pass to this reactive center through the mechanism of the blood system and that there should be no essential difference in the type of death but only a difference in the duration of the reaction. It seems likely that after intravenous injection the heart should be paralyzed before the medullary centers and that after subcutaneous injection the centers should be poisoned before the heart.

My experiments suggest, though they do not prove conclusively, that in both the sudden and the more prolonged type of reaction, death occurs chiefly from central medullary paralysis. The sudden and brief reaction which follows intravenous injection of a lethal dose of procaine is exactly like the terminal phase of the more prolonged reaction following subcutaneous injection of a lethal dose. In both there is so constantly an almost simultaneous cessation of respiration and heart beat that it suggests that the mechanism is likely to be a central one affecting both cardiac and respiratory centers. As has been mentioned previously, after subcutaneous injection the heart usually but not ininvariably beats for a short time after respirations cease, and vice versa, after intravenous injection the heart often but not always stops a moment before the last respiration. Sometimes the heart beats after respiration ceases, and if the thorax is opened soon after respirations cease, the heart is always found to be beating feebly even though clinically it was thought to have stopped. Convulsions are constant after subcutaneous injections of a lethal or near lethal dose and almost constant after intravenous injections. Only when an overwhelmingly large dose has been given intravenously, when death is practically instantaneous, are convulsions apt to be absent, and even then there is ordinarily a general extensor thrust as the animal dies. After a small intravenous injection there is a temporary drop in blood pressure, very transient and followed by a rise to a higher than normal level. This observation suggests that procaine may stimulate output of adrenalin. When a low concentration of procaine is achieved by slow absorption, this fall in blood pressure is not observed. It has been noted that a very small intravenous injection of procaine causes no fall in blood pressure but an actual increase. It is possible that with slow continuous absorption into the blood stream of small amounts of procaine there is the initial rise, and that as the blood procaine level rises, through some physiologic adjustment the blood pressure continues normal or elevated. Only when a high enough concentration has been achieved to constitute a fatal level does the blood pressure fall precipitously, along with failure of heart and respiration. Apparently, levels of blood procaine concentration insufficient to cause the fatal collapse are sufficient to bring about stimulation of respiration, increase in pulse rate, alteration in the state of consciousness, and convulsions.

In order to see whether, regardless of the route of administration and the size of the dose required to cause death by the different routes, the animals die with roughly the same blood procaine levels, such determinations were made in a number of animals poisoned by procaine administered by different routes. Blood for assay was removed from the heart immediately after death. In Table I are summarized the results of this study and in Fig. 4 are illustrated the range in blood procaine levels according to the route and amount of procaine injected. It will

be seen that after intravenous, intrapleural, intramuscular, and subcutaneous injections, although the injected dose varied from 40 to 500 mg. per kilogram of body weight, the average unchanged procaine level was almost identically the same. Somewhat more variation occurred in the estimated total procaine levels, more of the acetylated procaine being present after subcutaneous injections. Following intraperitoneal injections the procaine levels at death were somewhat higher. Whether this observation means that much of the procaine was absorbed into the portal circulation and that perhaps some of that estimated as unchanged procaine was actually rendered innocuous during passage through the liver, I cannot say. It is possible that where procaine is freely passing

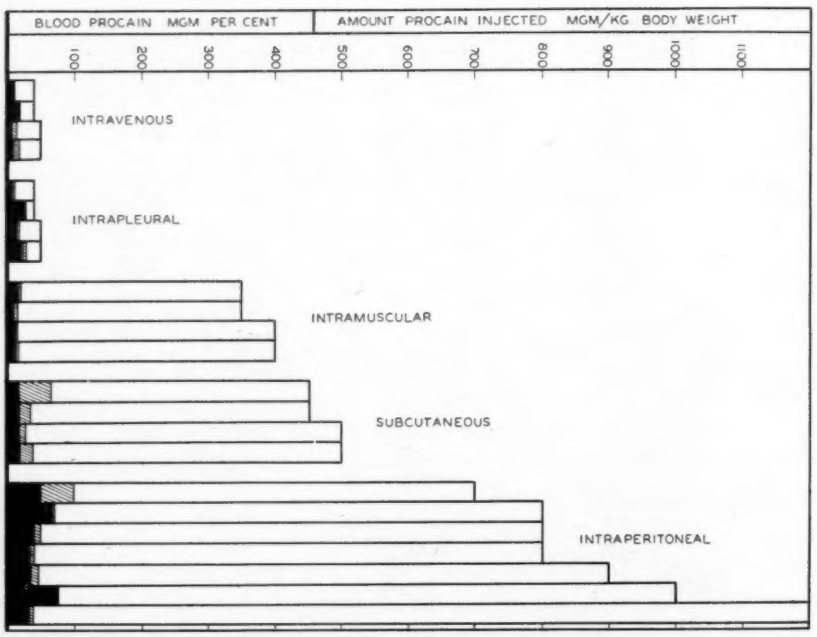

Fig. 4.—Chart showing blood procaine concentration at death according to the route and the amount of procaine administered. The unshaded columns represent amount of procaine injected in milligrams per kilogram of body weight. Shaded columns represent free blood procaine in milligrams per cent; cross-hatched columns represent total procaine concentration in milligrams per cent; where there is no crosshatching the free and total procaine concentrations were approximately equal.

into the blood system from such a large store, absorption may continue during the terminal period of antemortal collapse and thus raise the blood procaine level at death to a higher level than was actually present when the fatal reaction was induced. Altogether these studies seem to substantiate the idea that regardless of the route of administration, death depends upon the presence in the blood stream of a lethal concentration which is roughly the same regardless of its source.

It has been found repeatedly that the intravenous lethal dose of procaine and of other local anesthetics in experimental animals is considerably less than is the subcutaneous lethal dose. It seemed wise to

TABLE I

BLOOD PROCAINE LEVELS AT DEATH FOLLOWING ADMINISTRATION BY DIFFERENT ROUTES

ROUTE OF ADMINISTRATION	PROCAINE IN MG. PER KG. BODY WEIGHT INJECTED (AVERAGE)	FREE BLOOD PROCAINE IN MG. PER 100 C.C. (AVERAGE)	TOTAL BLOOD PROCAIN IN MG. PER 100 C.C. (AVERAGE)
Intravenous	45	11.5	14.4
Intrapleural	45	16.4	20.2
Intramuscular	375	11.0	15.6
Subcutaneous	475	15.7	40.7
Intraperitoneal	887	46.3	58.2

investigate in experimental animals the lethal dose of procaine administered by still other routes by which it might be deliberately or inadvertently injected into human patients. In Table II the data are summarized. Because the median lethal dose is much more accurate than an attempted estimate of the minimum lethal dose, results have been calculated in terms of the median lethal dose.[12] It will be seen that the intravenous median lethal dose is only one-tenth of the subcutaneous median lethal dose. Surprisingly enough, the intrapleural median lethal dose is almost as small as the intravenous, and it may be remarked that

TABLE II

SHOWING VARIATION IN MEDIAN LETHAL DOSE OF PROCAINE IN GUINEA PIGS ACCORDING TO ROUTE OF ADMINISTRATION AND ACCORDING TO AGE OF SUBJECT

ROUTE OF ADMINISTRATION	ALL ANIMALS*	YOUNG ANIMALS	OLD ANIMALS
Intravenous	41 (54)	41.5 (38)	38.5 (16)
Intrapleural	42 (25)	42 (15)	42 (10)
Paravertebral (thoracic)	115 (10)	115 (10)	
Paravertebral (lumbar)	250 (30)	280 (20)	213 (10)
Intramuscular	330 (25)	350 (15)	270 (10)
Subcutaneous	410 (56)	425 (47)	340 (9)
Intraperitoneal	750 (28)	765 (20)	725 (8)

*The number in parenthesis indicates the number of animals used in each series.

death occurs almost as rapidly after an intrapleural injection as after an intravenous injection, and in just the same manner. Control intrapleural injection of similar quantities of normal salt solution produced no symptoms. When procaine is deposited in the thoracic paravertebral region, the median lethal dose is also remarkably small, being roughly one-fourth of the subcutaneous median lethal dose. In this series the accuracy of the injection was proved by autopsy inspection, the procaine having been colored with a dye. Animals in which the injection was either too superficial or partly intrapleural were excluded. The lumbar paravertebral median lethal dose is somewhat larger but still only a little more than one-half of the subcutaneous. The intramuscular median lethal dose is a little less than the subcutaneous. Again, surprisingly enough, the intraperitoneal median lethal dose is almost twice as large

as the subcutaneous. In general it may be said that the larger the median lethal dose, the longer the period of survival. Others have demonstrated that if procaine is *slowly* injected intravenously, the animal will survive considerably larger amounts than if it is administered with great rapidity.[2] This fact is undoubtedly due to the rapid destruction or detoxification of the procaine, which Hatcher and Eggleston believe takes place in the liver.[2] From this fact and from what I believe to be true as regards the fatal blood procaine level, I think the enormous differences which exist in the median lethal dose according to the route of administration are due to differences in the rate of absorption of procaine from the various tissues and body cavities. With the intraperitoneal injections another factor may possibly enter into consideration; namely, the absorption of some of the material into the portal circulation and its detoxification in the liver. Perhaps the presence of large lymphatic collecting trunks in the paravertebral region may contribute to the relatively rapid absorption from this area, and in the thoracic paravertebral region, diffusion through the pleura may be an added factor. The entire question of the rate of absorption of procaine and other substances from various body tissues will be the subject of a further report. Regardless of the mechanism, the importance of these observations in the clinical use of procaine is immediately apparent.

The statement has been made that procaine should be used in more guarded amounts in patients in poor physical condition than in those in vigorous health.[4] The question arises whether age is also a factor in the toxicity of procaine. Having on hand a number of guinea pigs about a year older than those ordinarily available, I thought it advisable to put this question to the test of experiment. The results are given in Table II. With the exception of the intravenous and intrapleural routes, the median lethal dose is somewhat smaller in the older group regardless of how the procaine is administered. The differences, however, are not great.

It is commonly believed that all local anesthetics should be used in the most dilute solutions that are satisfactory. In Table III are summarized the data concerning this point. It is seen that slightly larger

TABLE III

SHOWING EFFECT OF CONCENTRATION OF INJECTED PROCAINE SOLUTION UPON MEDIAN LETHAL DOSE IN GUINEA PIGS

ROUTE OF ADMINISTRATION	0.5% SOLUTION*	1% SOLUTION	10% SOLUTION
Intravenous	47 (16)	40 (8)	38 (30)
Subcutaneous		470 (16)	385 (10)

*The number in parenthesis indicates the number of animals used in each group.

amounts of the more dilute solutions are tolerated. The differences are small and are, I believe, dependent upon the fact that the larger amounts of the more dilute solutions are necessarily injected more slowly in the

intravenous injections and are absorbed more slowly from the subcutaneous tissues than are the smaller amounts of the more concentrated solutions. Clinically, of course, a much more important consideration is this: ordinarily in infiltration anesthesia as large an amount of a concentrated solution will be required to obtain anesthesia as of a more dilute solution, and consequently the total amount of procaine used is apt to be much greater in the concentrated solution.

Since procaine is often used as a supplementary anesthesia during general anesthesia, I have studied the lethal properties of procaine given during ether anesthesia. Knoefel, Herwick, and Loevenhart[8] had observed in dogs that preliminary administration of morphine and rectal ether might reduce the symptoms of cocaine poisoning but was of no value in preventing death and that, indeed, with its use death might ensue with a sublethal dose. Tatum, Atkinson, and Collins[13] had previously found the inhalation of ether of no therapeutic value in cocaine poisoning. In my experiments the median lethal dose of procaine after ether anesthesia was determined in sixteen guinea pigs. The animals were kept asleep for five minutes with ether, the mask was removed, and varying amounts of procaine were injected intravenously. Under these circumstances, the median lethal dose was found to be only 15 mg. per kilogram of body weight in comparison with 41 mg. in the unanesthetized control animals. An effort was made to see whether the subcutaneous lethal dose was similarly reduced in animals kept asleep with ether, but was not entirely satisfactory. The procaine reaction itself is more prolonged with subcutaneous injections and is associated with loss of consciousness, so that it was difficult to estimate how much ether to give and one was never quite certain whether the animal was actually anesthetized with ether. The impression was that the lethal dose was somewhat less than in the unanesthetized animals.

The one prophylactic measure about which there is general agreement is the use of the barbiturate group of drugs. This measure was first introduced by Hofvendahl[14] and has been supported by Tatum, Atkinson, and Collins,[13] and others. Downs and Eddy[15] thought that barbital increased the fatal dose of cocaine in rats by about 10 per cent. Knoefel and his co-workers[8] found that sodium barbital and paraldehyde increased the minimum subcutaneous lethal dose of cocaine in the rabbit from 100 to 150 mg. per kilogram and in the dog from 26 to 100 mg. per kilogram, and that monkeys which died from 30 mg. per kilogram survived as much as 100 mg. per kilogram if barbital and paraldehyde were given beforehand.

Since I had obtained data concerning the reduction of the subcutaneous median lethal dose in guinea pigs if the procaine was introduced by other routes, I thought it important to see just how much the median lethal dose could be increased through the prophylactic use of

one of the barbiturates. Maloney[9] has shown that the most effective barbiturates are those of high toxicity such as nembutal, dial, and pernocton. In these experiments nembutal was used, each animal being given 0.8 c.c. per kilogram of body weight of a 4.2 per cent solution intraperitoneally twenty minutes before administration of the procaine. The animals were sound asleep, almost completely anesthetized. The dose was safe as determined with a number of control animals. The results are summarized in Table IV. The intravenous and the intrapleural median lethal doses were not increased but were actually decreased somewhat; the intramuscular and subcutaneous median lethal doses were increased by about 70 per cent.

TABLE IV

SHOWING PROPHYLACTIC EFFECT OF NEMBUTAL ON MEDIAN LETHAL DOSE OF PROCAINE IN GUINEA PIGS

ROUTE OF ADMINISTRATION OF PROCAINE	NEMBUTAL GIVEN BEFORE PROCAINE*	UNTREATED CONTROLS
Intravenous	35 (10)	41.5 (38)
Intrapleural	35 (12)	42 (15)
Intramuscular	610 (16)	350 (15)
Subcutaneous	700 (16)	425 (47)

*The numbers in parenthesis indicate the number of animals used in each group.

Although the barbiturates are of some aid in the prophylaxis and treatment of local anesthetic overdosage when absorption is slow, they are of no aid in preventing or treating the reactions which follow rapid absorption of a toxic dose. No very satisfactory treatment for such reactions has been demonstrated. In ten guinea pigs given 50 mg. per kilograms of procaine intravenously, 0.05 c.c. of coramine given intravenously immediately thereafter did not save a single animal. Five-hundredths cubic centimeter of coramine was determined on control animals to be a safe dose; 0.08 c.c. caused convulsions. Similarly, ten guinea pigs given 50 mg. per kilogram of procaine intravenously could not be saved by the intravenous injection immediately thereafter of 0.025 c.c. of metrazol, although the heart beat and respirations continued perhaps a moment or so longer than usual. Even when the metrazol was mixed with the procaine before injection, none of the animals survived. Artificial respiration in these animals did not prevent death. The amount of metrazol used was found by injections into control animals to be a safe dose.

DISCUSSION AND SUMMARY

It appears likely from the data presented as well as from certain material in the literature that all or nearly all of the symptoms arising from an overdose of procaine are due to affection of the nervous system and chiefly to affection of the central nervous system. Death is probably due essentially to medullary respiratory and cardiac paralysis.

There is no significant reduction in plasma volume during procaine reactions. The essential difference between the types of reaction that follow rapid absorption or direct intravenous injection of procaine on the one hand, and slow absorption from the subcutaneous or other tissues on the other, seems to be the duration of the reaction. The terminal failure of vital functions appears to be the same in both types. Death seems to be contingent upon a certain critical concentration of procaine in the blood, varying somewhat in individuals, but in general being of roughly the same order.

The lethal dose of procaine varies widely according to the route of administration. The intravenous median lethal dose is only one-tenth as great as the subcutaneous, and the intrapleural median lethal dose about the same. The thoracic paravertebral median lethal dose is little more than one-fourth as large as the subcutaneous, and the lumbar paravertebral about one-half as large. The intramuscular median lethal dose is somewhat smaller than the subcutaneous, and the intraperitoneal almost twice as large. These enormous differences in toxicity of procaine with different routes of administration are probably due to differences in the rate of absorption of the drug. It is obvious from these data that one should be very careful not to inject procaine intravenously or intrapleurally. In paravertebral injections, especially in the thoracic region, only small amounts of procaine should be used. One need not be concerned about the injection of moderate amounts of procaine into the peritoneal cavity.

A given amount of procaine is somewhat more toxic if administered in a concentrated solution than in a dilute solution, probably because of the more rapid absorption of the former. A more practically important reason for using only dilute solutions is the fact that satisfactory anesthesia can frequently be obtained with an actually smaller amount of procaine if a dilute solution is used. Anything that slows the absorption of procaine makes it safer. Others[2] have demonstrated that adrenalin mixed with procaine brings about an increase in tolerance to the drug through slowing the rate of absorption.

The old appear to tolerate procaine somewhat less well than the young. Other conditions which seem to decrease tolerance are severe hemorrhage[2] and probably damage to the liver, since procaine is thought to be largely detoxified in this organ.[2] Ether anesthesia definitely decreases the lethal dose of procaine given intravenously and probably also if given by other routes.

As regards prophylactic and therapeutic measures the experimental literature is full of contradictions. Salent and Nadler[17] thought alkalies given intravenously before cocaine increased the tolerance to the drugs in cats, and Knoefel and co-workers[8] found them of no value in cocaine poisoning by intravenous injection in dogs and rabbits, nor did Eggleston and Hatcher[2] find them of any value in saving cats after intravenous

injections of various local anesthetics. Eggleston and Hatcher[2] found that caffeine had no prophylactic influence on the toxicity of intravenously injected local anesthetics, but Nielsen and Higgins[18] found it of a little value in counteracting the effects of subcutaneously administered butyn. Dragstedt and Lang[19] thought atropine of some prophylactic value, but Knoefel and his co-workers[8] found that it did not influence the outcome in cocaine poisoning in rabbits following subcutaneous injections, nor did Eggleston and Hatcher[2] find it of value in intravenous injections of various local anesthetics in cats. Knoefel and associates[8] found ephedrine of no prophylactic value and Nielsen and Higgins[18] found it of questionable value. Eggleston and Hatcher[2] thought adrenalin combined with artificial respiration of definite therapeutic value in cats poisoned with cocaine injected intravenously. Nielsen and Higgins[18] thought pituitary solution of prophylactic and therapeutic value in rabbits and dogs poisoned with butyn given subcutaneously, but Knoefel and his co-workers[8] thought it of no value in cocaine poisoning in cats and dogs. Eggleston and Hatcher[2] thought ouabain of prophylactic value before intravenous injections of various local anesthetics in cats, but Knoefel and his co-workers[8] found it did not help with intravenous injection of cocaine in a few dogs and cats. Hyoscine, morphine, morphine and rectal ether, chloral hydrate, potassium cyanide, amyl nitrite, intravenous saline solution, and calcium appear to be without value.[2, 8, 10, 18] Tatum and Collins[16] found artificial respiration efficacious in treating rabbits injected subcutaneously with cocaine, but not dogs. With cats given toxic doses of various local anesthetics intravenously, Eggleston and Hatcher[2] found artificial respiration alone or combined with cardiac massage of no aid, but of value combined with the intravenous administration of adrenalin.

The outstanding observation about which there is general agreement is that the barbiturates seem to be of value prophylactically and therapeutically against subcutaneously administered local anesthetic agents.[8, 9, 13-16] The higher the animal as regards brain development, the more effective the barbiturates seem to be. The ideal barbiturate is apparently one combining high toxicity and long-continued action.[9] Tatum, Atkinson, and Collins[13] are of the opinion that the deleterious effect of the local anesthetic on the respiratory center is by way of the cerebrum and that essentially a tetany of the respiratory center with ultimate exhaustion occurs. They feel that the barbiturates are effective through depressing the higher functions of the brain as well as the respiratory center. Whether this is the correct explanation I cannot say. Nor can I explain why only the barbiturates are effective and apparently no other central nervous system depressants, sedatives, and hypnotics; for example, morphine, ether, chloral hydrate, etc. Nor can I explain why the barbiturates are effective against local anesthetics

slowly absorbed, but not when rapidly absorbed; that, indeed, in the latter case tolerance may be decreased. The explanation of Knoefel and his co-workers[8] that this is due to the direct action of the anesthetic on the heart does not seem entirely satisfactory.

In the present study it was found that nembutal given before procaine increased tolerance about 70 per cent when the procaine was given subcutaneously or intramuscularly, but decreased tolerance slightly when the procaine was given intravenously or intrapleurally.

I was unable to save animals given procaine intravenously by the intravenous administration of coramine or metrazol.

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REACTIONS TO LOCAL ANESTHETIC AGENTS

II. A Clinical Report

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COCAINE was first used as an agent for inducing local anesthesia following the discovery of its anesthetic properties by von Anrep[1] in 1880 and its applicability in ophthalmological surgery through the experimental and clinical observations of Koller.[2] Hardly had its use been well established in surgical practice before the necessity for substitutes arose because of the habit-forming property of this drug and especially because of the too common reactions which followed its use. These reactions were frequently mild in character and recovery ensued, but too often they were severe and even fatal.

A dozen or more substitutes were introduced, all alike in some respects and each with certain virtues and defects. They are all, like cocaine, lipoid soluble alkaloids. None is habit forming. They vary in effectiveness when topically applied to mucous membranes, in the duration of anesthesia, and in other respects. It is not within the province of this report, however, to discuss the relative merits or the special field of application of each of these anesthetic agents. Suffice it to say, first, that for nerve blocking and local infiltration there is general agreement that procaine is reliable, effective, and the safest of all these agents; and second, that cocaine and the entire group of cocainelike anesthetics are similar in the types of reaction which they may evoke, although they differ in the frequency with which their use is attended by such an untoward effect.[3-7]

It is my purpose to discuss these reactions in regard to their character, prevention, and treatment and to describe some illustrative cases which have occurred in the Johns Hopkins Hospital. I shall limit myself to reactions following the use of these agents in topical application, local infiltration, and nerve blocking. I shall not consider the reactions which occasionally follow spinal anesthesia since there is good evidence that they are ordinarily to be ascribed to the anesthesia obtained rather than to idiosyncrasy or to overdosage of the drug. For like reason I shall exclude reactions following caudal anesthesia. In one recent fatal case in the Johns Hopkins Hospital the anesthetic had been inadvertently injected into the subarachnoid space, as was proved by analysis of the cerebrospinal fluid.

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

About twenty years ago the American Medical Association's Committee for the Study of Toxic Effects of Local Anesthetics asked that all reactions be reported to it, and in 1924 and again in 1928 Mayer published the fatal cases which had been submitted.[5, 8] Among other recommendations the request was made that all severe and fatal reactions be recorded in the literature. Few such cases have been reported. Whether this is indicative of the extreme infrequency of these reactions or to a failure to report them, I do not know. If the latter is the case, we may be lulled into a false sense of security. To call them to the attention of the medical profession need cause no undue alarm nor undermine the correct general impression as to the relative safety of local anesthesia, and yet may keep us alive to the possibility of their occurrence, and make us more alert in utilizing the known safeguards in an effort to prevent them and better prepared to treat them once they occur. Furthermore, discussion may stimulate experimentation which may lead to better prophylaxis and treatment. It is with these ideas in mind that I submit this report.

The reactions may be divided into two types; first, those presumably dependent upon true hypersensitivity of the patient to the drug; and second, those resulting from absorption of a toxic dose. The following are examples of the first type of reaction.

CASE 1.—A minute amount of novocaine was injected into the skin of a patient preparatory to a lumbar puncture.* The injection had hardly been made before the patient began to wheeze in a typical asthmatic attack. She immediately asked the physician whether he had not injected novocaine, telling him that her only other attack of asthma had followed injection of this drug. She did not have hay fever or allergy to any of the common antigens. Before epinephrine could be secured and administered the brief but momentarily alarming attack had subsided.

MacKay[9] reported a somewhat similar reaction in a tuberculous patient who had wheezing, labored breathing, feeling of tightness in the mediastinum, weak and rapid pulse, and prostration after each pneumothorax refill done with local novocaine infiltration: She had had some wheezing before, independent of the refills, and this continued, but had no reactions following her refills when they were carried out without anesthesia.

CASE 2.—(Unit No. 124977.) The patient, a 25-year-old medical student, had incision of two small chalazions on the lower lid and a small hordeolum on the upper lid of the right eye after instillation with 1 per cent pontocaine solution. Two days later he had extreme swelling and injection of the conjunctivae of the right eye. The following day the chemosis and conjunctival injection were very great and the face was puffy about the outer canthus. There was little discharge, and smear and culture were negative. He was admitted to the hospital but the frequent use of argyrol and boric acid followed by irrigations of zinc sulfate brought about no

*Cited to me by Dr. Paul Padget of the Department of Medicine, Johns Hopkins University.

improvement. In fact, the reaction proceeded to a point where there was actually some loss of substance. Pontocaine reaction was finally suspected, and eight days after the operation a skin sensitivity test was carried out, 0.1 c.c. of 1 per cent procaine being injected intradermally into one arm and the same amount of 0.5 per cent pontocaine into the other. He had no reaction to the procaine, but a violent reaction to the pontocaine. In twenty-four hours the area of reaction measured 6 by 10 cm. and there was some necrosis in the central portion. Both the ocular and the cutaneous reaction subsided slowly, and he was discharged seventeen days after the operation.*

A case similar to this one has been reported by Pfeiffer,[10] and the same general sort of reaction has been encountered by others. One of MacKay's[9] tuberculous patients had pain locally after each pneumothorax refill with novocaine anesthesia and remained entirely free of this local soreness when these treatments were carried out without anesthesia. Mullen[11] recorded two similar cases of local pain, tenderness, erythema, and induration after each refill, with complete absence of such reaction when the refills were done without novocaine. A skin test in the arm with 0.1 c.c. of novocaine in each case resulted in a typical local reaction.

It seems entirely likely that reactions of these sorts represent a true hypersensitivity to the drug. I know of no experimental production of these reactions. Epinephrine or ephedrine should be of some aid in treating them.

The reactions which are ascribed to a toxic dose may be mild or severe. In the mild reactions there may be restlessness, palpitations, perspiration, pallor, loquacity, nausea, and tremor. There is good evidence that the incidence of such reactions may be substantially reduced by preliminary medication with one of the barbiturates and that the reactions may likewise be successfully treated with barbiturates.[12-15] The severer reactions are generally divided into two groups, one characterized by convulsions and respiratory failure, the other by sudden collapse. In the former there may be apprehension, excitement, delirium, and dyspnea. There are always convulsions, and death is ordinarily said to be respiratory in type. The second group is associated with sudden pallor, tachycardia, fainting, and shock. Cardiac and respiratory failure occurs very rapidly. I am not entirely certain that death in the first type is primarily due to respiratory and in the second to cardiac failure,[16] as is commonly believed. The barbiturates are apparently effective prophylactically and therapeutically in the first type of reaction, but of no value in the second.[13-18]

These reactions are exemplified by the following cases which have occurred in the Johns Hopkins Hospital. One death occurred with cocaine, two with butyn and cocaine, and one with procaine. Three additional nonfatal procaine reactions are included.

*This case is reported through the courtesy of Dr. J. M. McLean.

CASE 3.—(Unit No. F 52324.) The patient, a colored male, 32 years of age, came to the Rectal Clinic in 1916 complaining of bleeding hemorrhoids. Nothing else of consequence was found in the history or on physical examination. He returned a few days later for hemorrhoidectomy under local quinine-urea anesthesia. With the patient in the knee-chest position, the area was properly prepared and local infiltration was carried out, 25 c.c. of the anesthetic solution being used. The injection was hardly completed when the patient suddenly cried out in an incoherent manner, fell forward on his face, and began frothing at the mouth. He rapidly lost consciousness and had several violent clonic and tonic convulsions. In spite of attempts at artificial respiration it was impossible to restore pulse or respirations, which had rapidly disappeared; the patient did not regain consciousness and died within about five minutes. On analysis of the anesthetic solution it was found that by mistake the operator had been given 10 per cent cocaine.

CASE 4.—(Unit No. J 76779.) The patient was a white male, 72 years of age, who came to the Nose and Throat Dispensary in 1931 because of hoarseness of six months' duration. He was found to have a carcinoma of the larynx. After a preliminary spray with 5 per cent butyn, cocainization of the larynx with a 20 per cent solution was begun in preparation for biopsy. During this procedure he began to complain of being short of breath, and quickly stopped breathing. A tracheotomy and artificial respiration were of no avail. A note records that the heart continued to beat at least five minutes after respirations ceased.

CASE 5.—(Unit No. 175032.) The patient, a 43-year-old male, was admitted to the hospital in June, 1939, with a carcinoma of the lung for which a total pneumonectomy on the right side was performed. An empyema associated with a bronchial fistula developed and was treated by drainage with an intercostal catheter and bronchoscopic applications of silver nitrate. He was discharged in September, and returned in October and again in November for bronchoscopy. On the latter occasion his larynx was cocainized with application of 20 per cent cocaine after a preliminary spray with 5 per cent butyn. As soon as this preparation had been completed and he was placed on the bronchoscopic table, he complained of shortness of breath and suddenly had a generalized convulsion. The mouth was quickly forced open and the bronchoscope passed, through which oxygen was delivered. He rapidly lost consciousness, the convulsive seizure persisted, and after about twenty minutes respirations ceased. Although the clinical note makes no mention of it, one of those present thinks that adrenalin was given intravenously. The patient had been similarly cocainized for four previous bronchoscopic treatments without reaction.

CASE 6.—(Unit No. 196469.) A white female, 50 years of age, who had had an arthrodesis on the left hip for traumatic arthritis, was readmitted in July, 1940, about five weeks after discharge, because of pain in the leg and thigh, which was still in a recently applied spica cast. It was thought that she had a thrombophlebitis, and a paravertebral sympathetic block with 2 per cent procaine was carried out. Almost immediately she had a severe reaction characterized by pallor, rapid pulse, and faintness. She was given 2 c.c. of metrazol intravenously and prompt recovery ensued.

CASE 7.—(Unit No. 206971.) A 52-year-old white male was admitted in August, 1940, with femoral thrombophlebitis. A lumbar paravertebral sympathetic block was carried out with 2 per cent procaine. About 4 c.c. each was injected at the level of the first, second, and third lumbar ganglia. The total amount used is not stated, but was thought by the operator to have been 20 or 30 c.c. Five or ten minutes after the injection the patient felt faint and nauseated, the pulse became

rapid and thready, and blood pressure fell to about 50 systolic. He was given 0.5 c.c. of caffeine sodium benzoate intramuscularly and 4 c.c. of coramine intravenously. His symptoms and the signs of shock persisted for almost two hours. Recovery followed.

CASE 8.—(Unit No. 169098.) The patient, a 7-year-old colored girl, came to the Accident Room in September, 1940, with a Y-shaped laceration of the right arm which she had sustained in a fall. Some of the fibers of the triceps muscle had been divided. The surrounding area was prepared with kalmarid and infiltrated with about 15 c.c. of 2 per cent procaine, after which the wound itself was cleaned with surgical detergent and kalmarid. Some bleeding started, a tourniquet was applied, and repair was begun. After the muscle was approximated and suture of the skin was begun, the patient suddenly became apneic and respirations ceased. She could not be roused, and the pulse was very rapid though it felt of normal volume. Artificial respiration was begun. After about two minutes she began to gasp for air in short respiratory excursions. Respirations became normal after a few minutes though she did not respond for several minutes more. About ten minutes after the reaction began she appeared normal.

CASE 9.—(Unit No. 208659.) A 40-year-old white female was admitted in August, 1940, because of Raynaud's disease and scleroderma. The following day skin temperature studies and a dorsal procaine block were done. Six cubic centimeters of 2 per cent procaine was used in infiltrating the skin and the subcutaneous and intramuscular tissues. The needle was introduced paravertebrally about fifteen minutes after the injection was begun. Ten cubic centimeters of procaine was now injected, 2 c.c. at a time. Almost immediately the patient said she felt a little faint, and she was allowed to lie down. She said she still felt faint. The pulse seemed of normal volume and was not increased in rate. Suddenly, five minutes after the injection, she lost consciousness, the pulse disappeared, and heart and respirations ceased, all about simultaneously. The foot of the bed was quickly elevated, and coramine, caffeine, and adrenalin were given intravenously in rapid succession. Artificial respiration was begun with oxygen inhalation. Coramine was again given intravenously, and when no response was obtained, 4 c.c. was injected into the heart. An artificial respirator delivering oxygen was by now in use. Suddenly, fourteen minutes after the collapse occurred, she began to breathe spontaneously, the radial pulse became perceptible, and the heart sounds were fairly vigorous. Her face, however, remained cyanotic. After five minutes, heart and respirations ceased as suddenly as they had reappeared. During the last few minutes there was a little frothing at the mouth. During the reaction she had had several hundred cubic centimeters of 5 per cent glucose and normal saline solution intravenously. At the end coramine was again injected into the heart, but without effect.

Since the few centimeters of procaine remaining in the flask had been spilled during the procedure, none remained for testing. The batch of procaine solution of which this was a sample, however, caused no other reactions. The injection was carried out with a 2 c.c. syringe. Each time the syringe was removed for refilling no blood and no spinal fluid was seen at the open end, and there was no sucking in of air. Each injection was preceded by attempted aspiration; no blood, spinal fluid, nor air was withdrawn. During the five minutes when the patient was breathing there was ample evidence that no high spinal anesthesia had been obtained. This fact is mentioned because in an attempted sympathetic block it is possible to inject the fluid into the subarachnoid space. As White has pointed out,[19] this accident is more likely to happen if the needle is directed cephalad, but this was not the case in this instance. In neither this nor the other two cases was there any evidence that a subarachnoid, intravenous, intrapleural, or intraperitoneal injection had been made, and the usual care had been exercised to guard against these possibilities.

In neither this nor the other cases was adrenalin used with the procaine.

It will be noted that one of the cocaine and all of the procaine reactions occurred within the past year. I am unable to find in the hospital records other cases of severe or fatal reactions to local anesthetics. This fact does not necessarily mean that none has occurred. Unfortunately, because of possible failure to include these diagnoses in the index files, any that may have occurred cannot be traced. Undoubtedly other nonfatal reactions have occurred. If other fatal reactions have escaped detection, they must be few in number.

It is extremely unfortunate that in none of the fatal cases was autopsy permission obtained, although it is true that in autopsies on other patients who died apparently of such reactions, nothing significant has been observed. Hatcher and Eggleston[20] have suggested that in cases where small amounts of novocaine have been used, death may possibly be due to some abnormality of the heart or respiratory center whereby susceptibility to the toxic action of the drug is increased to an extraordinary degree. Follis[21] has recently reported cases which suggest that sudden death during general anesthesia may be at least partly dependent upon some anomaly of the coronary vessels. It is equally unfortunate that blood was not drawn at death for determination of blood procaine concentration, as such studies might throw some interesting light upon the subject.[16]

In connection with this general problem of reaction, certain questions naturally arise. In the first place, one would like to know what constitutes the essential difference between the so-called "convulsive-respiratory failure" and "collapse" types of reaction. In my experiments[16] the sudden deaths where the procaine was injected directly into the blood or was absorbed with great rapidity more nearly resembled those clinical reactions designated as the collapse type, and the more prolonged reactions resulting from injection of a fatal dose subcutaneously or by some other route where absorption is slow were more like those clinical reactions designated as the convulsive type. Except for the time interval before the onset of the reaction and for the duration of the reaction, no essential difference was noted. Even where the reaction was prolonged the terminal phase resembled remarkably the briefer reactions. The work suggested, though the point could not be definitely proved, that in all instances death was primarily due to central medullary cardiac and respiratory paralysis. In all the experimental reactions convulsions were the rule. Clinically, the collapse type of reaction is said to be characterized by circulatory failure and death from cardiac failure. This is certainly not always true. In Case 4 there was a sudden collapse and rapid death, associated with no convulsions, and yet the heart continued to beat after respirations ceased; and in Case 9, where the initial symptom was a feeling of faintness, heart and respirations ceased simultaneously, began again simultaneously during the brief

period of resuscitation, and again ceased at the same instant.* It is said that the collapse type of reaction is either accompanied by no convulsions at all or by a single convulsion. In Case 3, where sudden collapse occurred and death took place within the short space of five minutes, there were vigorous convulsions up to the end. As a matter of fact, one would have difficulty in fitting a number of the cases I have reported into either the one category or the other according to the usual descriptions. One must suspect that in human beings, as in laboratory animals, the important factor is the rate of absorption and the amount of the anesthetic absorbed, and that upon these factors depend the duration and the character of the reaction.

Second, one would like to know what constitutes a "safe" dose. This question it is impossible to answer. Liebel[22] injected into himself 400 mg. of 1 per cent novocaine and an hour later 750 mg., without ill effect. Braun[23] used clinically as much as 1,500 mg. of procaine in 0.5 or 1 per cent solution, without reaction. Siegel[24] used 3,000 mg. of 0.5 per cent novocaine, without reaction. Bieter[7] suggested 430 mg. as a safe dose and one-half as much in highly vascular areas. Labat,[6] who had a vast experience, gives as a maximal safe dose 2,500 mg. of 0.5 per cent novocaine, 1,500 mg. of 1 per cent, and 1,200 mg. of 2 per cent. These estimates are chiefly on a basis of clinical experience. The death from procaine poisoning which I have reported occurred following the use of 320 mg. As little as 30, 20, and even 12.5 mg. have resulted in fatalities.[5, 20] It is apparent that the "safe" dose is unknown and that what is a safe dose in the majority of cases may in a rare instance prove fatal. In addition to route of administration and rapidity of absorption, which influence the toxicity and which I shall discuss later, it is clear that in certain fatalities a true idiosyncrasy must occasionally be taken into consideration.

Another question concerns the concentration of the anesthetic solution. The general belief is that one should use as dilute a solution as is satisfactory. Mayer[8] felt that procaine should be given in no greater concentration than 1 per cent; Labat,[6] Bieter,[7] and others, in no more than 2 per cent. Labat[6] suggested that the actual amount of novocaine which constitutes a safe maximal dose may be twice as much in 0.5 as in 2 per cent solution. Experimental animals tolerate slightly larger amounts of procaine if it is given in dilute solution, probably because the larger amounts of the more dilute solutions are absorbed more slowly.[16] It is well known that much more than an ordinary intravenous lethal dose may be injected without causing death if the solution is injected slowly.[24] There are other valid reasons why dilute solutions should be used. Anesthesia is likely to be obtained with an actually smaller amount of the

*In the procaine reactions which were not fatal, two (Cases 6 and 7), were characterized by circulatory collapse, but one (Case 8) was characterized primarily by sudden cessation of respirations and loss of consciousness.

anesthetic if a dilute solution is employed for the reason that in ordinary infiltration a certain volume is almost sure to be necessary to obtain satisfactory anesthesia regardless of its concentration; also, if some of it were to be inadvertently injected into the blood stream, it would be much less apt to prove fatal if a dilute solution were being used. Likewise, except where specifically contraindicated, adrenalin should always be mixed with the anesthetic solution because this combination both slows the rate of absorption and increases the duration of the anesthesia.[25] The sole advantage of using a more concentrated solution seems to be that the duration of anesthesia may be longer if the concentration is greater.

Still another question concerns the route of administration. It is striking that all three of the procaine reactions which I have reported followed paravertebral sympathetic block. I know of no other reported fatalities with this sort of injection. The technique used was that recommended by White[26] for dorsal and by Ochsner and DeBakey[27] for lumbar block, except that these authors used 1 per cent solution; whereas, in these cases 2 per cent was used. The actual amount of procaine given in the fatal case, however, was well within the limits of what is ordinarily considered a safe dose. As has been mentioned before, the usual precautions were observed to avoid inadvertent injection into the blood stream, subarachnoid fluid, peritoneum, or pleura. It has long been known that experimentally the intravenous lethal dose is much less than the subcutaneous. My experiments[16] with guinea pigs have revealed what I believe to be clinically important; namely, that the median lethal dose of procaine is only one-tenth of the subcutaneous if the solution is given either intravenously or intrapleurally, one-fourth if given in the thoracic paravertebral region, one-half in the lumbar paravertebral area, and about eight-tenths if given intramuscularly. If given intraperitoneally, however, the median lethal dose is about twice as large as the subcutaneous. It is believed that these differences are due to differences in the rates of absorption from the various tissues and body cavities. Obviously, then, one should use smaller amounts of anesthetic solutions in those tissues where the lethal dose is known to be small.

Certain other factors probably reduce the lethal dose somewhat. The old tolerate procaine slightly less well than the young.[16] Acute hemorrhage, circulatory depression, decrease in liver function, and other conditions which might interfere with the proper delivery of the procaine to the liver for detoxification or which might interfere with this process in the liver itself, probably decrease tolerance to procaine and the other anesthetic agents.[25] Ether anesthesia also probably decreases tolerance to procaine;[16] hence, one should be somewhat guarded in the amount used in supplementing general anesthesia.

Finally, another important question is how the reactions may be prevented and treated. The one agent which has been generally found of

value is the group of barbiturates. Experimentally, deep hypnosis approaching surgical anesthesia induced with one of the barbiturates definitely increases tolerance to the local anesthetics in a variety of animal species, provided the anesthetic is administered by a route where slow absorption takes place.[16] It appears that clinically moderate doses of the barbiturates are effectual in preventing the milder type of toxic reaction and the severer sort characterized by convulsive manifestations and rather prolonged duration. In experimental work the barbiturates are entirely ineffective in preventing reactions of the type which follow rapid absorption of the anesthetic; presumably also those clinical reactions which come on rapidly and terminate quickly and which are apparently the result of rapid absorption of a toxic dose, cannot be prevented by barbiturates. Those reactions, the incidence of which can apparently be reduced by preliminary administration of barbiturates, can sometimes be effectively treated by the intravenous administration of one of the barbiturates once the reaction has begun. It appears that the ideal barbiturate is one of high toxicity and long continued action.[17] Nembutal, dial, and pernocton have been demonstrated to be effectual. Seconal might prove valuable in prophylaxis, and sodium pentothal might be a useful agent in the treatment of these reactions. The reactions which follow rapid absorption are more difficult to treat. Experimentally, one investigator has found intravenous adrenalin and artificial respiration of value.[25] Pituitary solution has been reported to be effective in experimental reactions,[28] but others have found it disappointing.[29] In some of the clinical cases I have reported coramine and metrazol may have been of aid, although experimentally I could not demonstrate their efficacy.[16] Since preliminary administration of the barbiturates is not only ineffective in preventing reactions which follow rapid absorption of the anesthetic agent but may actually decrease the lethal dose of the agent,[16] it is all the more mandatory that every care be exercised to prevent injection into the blood stream or into tissues from which rapid absorption takes place.

From these considerations and others one might make certain suggestions, many of which have been emphasized by other workers.

1. Cocaine should never be given by injection. Urethral instillation of an anesthetic should not be made in the presence of trauma. Procaine is probably the most satisfactory anesthetic for infiltration or nerve blocking.

2. All anesthetics should be used in as dilute solution as is satisfactory; procaine should probably not be used in concentration greater than 1 per cent. Except where specifically contraindicated, adrenalin should always be used in the anesthetic solution. Injections should be made slowly and with care to avoid injection into the blood stream; an anesthetic should not be injected directly into the pleural cavity; and extreme care should be exercised as to the quantity of the anesthetic used

in paravertebral injections. It should be kept in mind that the fatal dose may be less in elderly and very ill patients and those with poor circulation and reduced liver function. Large amounts of local anesthetics should not be used in supplementing general anesthesia. All solutions should be properly labeled so that no mistake can be made as to what is being injected.

3. One of the barbiturates should be used as preliminary medication. If a reaction occurs which seems predominantly convulsive in character, and particularly if its onset suggests relatively slow absorption of the anesthetic, an intravenous injection of one of the barbiturates should be made. Until something more specifically helpful is learned, those reactions which come on rapidly and are associated with early collapse should probably be treated with intravenous injection of adrenalin and of one of the cardiorespiratory stimulants such as coramine or metrazol. If the pulse has disappeared, the injection should be made into the heart. If the respirations are compromised, artificial respiration and oxygen inhalation should be begun immediately. If a severe or fatal reaction occurs, an analysis of the anesthetic concentration in the blood should be carried out.

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THE MOBILIZATION AND DEPOSITION OF BONE CALCIUM BY ELECTROLYSIS

A Preliminary Report

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THE effect of electrolysis on bone has not been reported in recent medical literature. The following observations indicate that electrolytic action can modify tissue response about an electrode in contact with bone.

Two platinum bands were wrapped subperiosteally around the femur of an anesthetized rabbit. The bands were 2 mm. wide and were applied snugly to the cortex about 1 cm. apart. Their free ends were insulated

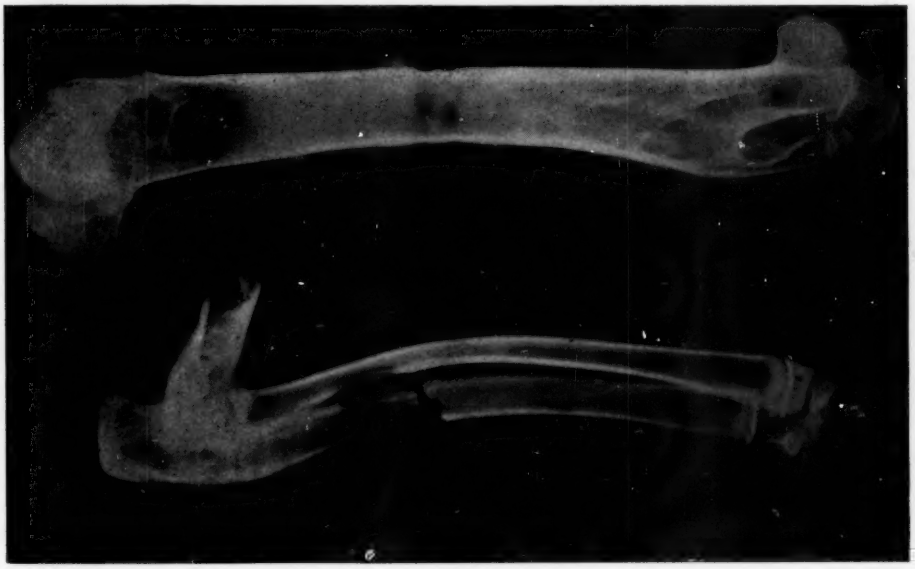

Fig. 1.—Femur illustrates mobilization of calcium from cortex underlying the positive electrode with deposition of calcium about the electrode. Ulna and radius show mobilization of calcium post mortem without redeposition.

with rubber and left projecting from the wound. During the fifth to eighth postoperative days a 1½ volt battery was connected to the bands for a total of about twenty-four hours. The rabbit was then sacrificed.

Examination of the excised femur revealed a shell of calcium-containing material bridging the positive electrode. The cortical bone at either end of this shell was roughened by adherent granular masses similar to

Received for publication, June 19, 1941.

early calcium deposition in callous about a fracture. When the positive platinum band was removed, parallel troughs 1.5 mm. wide were noted encircling the bone. These depressions corresponded roughly to the edge of the band. The cortex beneath the electrode was furrowed and rough. There was no gross reaction about the negative electrode.

Roentgenologic examination revealed transverse bands of decreased density underlying the region once occupied by the positive electrode. When seen tangentially, these bands appeared as distinct depressions in the cortex. A bridge of opaque material spanned the area described.

Control experiments showed that the electrodes themselves did not produce the changes described. The passage of current through electrodes applied loosely to bone produced no effect, indicating that the response is dependent upon the mobilization of calcium from the bone. Electrolysis mobilized calcium from the bone post mortem, but deposition in the dead soft tissues did not occur.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

HYPERTENSION AND UNILATERAL RENAL DISEASE

REVIEW OF THE LITERATURE AND REPORT OF 16 CASES

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(Continued from the June issue)

III. VASCULAR LESIONS AFFECTING THE KIDNEY.—A review of the literature reveals many pathologic reports of cases in which renal ischemia was produced or considerably influenced by lesions affecting the patency of the large and small renal arteries and the adjacent portion of the abdominal aorta. An accurate diagnosis is seldom made during the clinical course of these diseases but is usually established after post-mortem gross or microscopic study. The relationship of hypertension to the various vascular lesions has not been defined. In most instances renal ischemia of a localized or generalized type may ensue, but the pathogenesis of the hypertension in the given case may remain conjectural.

It is not my intention to participate in any controversial issues concerning the relation of hypertension to renal arterial disease but rather to relate in a chronological order pertinent facts and observations of the various investigators in order to establish a clearer understanding of the relation of hypertension to renal arterial disease. As early as 1836, prior to the development of blood pressure determinations, Richard Bright, in his classical work on chronic interstitial nephritis, pointed out the relation of renal disease to cardiac hypertrophy (i.e., hypertension) and recognized the thickening of the renal arterioles but did not emphasize the importance of physical changes in this process. It remained for Gull and Sutton in 1872 to demonstrate the occurrence of widespread organic disease of the smaller arteries, arterioles, and capillaries of the kidney, which they designated as "arteriocapillary fibrosis" and to consider these changes as the cause of hypertension and cardiac hypertrophy. In 1873, Johnson proposed a theory that the renal disease was primary with subsequent diffuse thickening of the walls of the smallest arteries leading to increased peripheral resistance, hypertension, and cardiac hypertrophy. Seven years later Ziegler first demonstrated the dependence of some forms of renal atrophy on arteriosclerosis of the larger renal arteries (arteriosclerotic contracted kidney).

Credit is due Jores in 1904 for first differentiating such forms of renal atrophy which were commonly called chronic interstitial nephritis but which were actually caused by arteriosclerosis of the smaller renal blood vessels. Four years later Jores advanced the theory that the diffuse fine granular kidney in chronic interstitial nephritis was also of a vascular atherosclerotic origin and that this type of renal atrophy was always accompanied by a marked hypertrophy of the left ventricle. Allbutt and Huchard stressed the frequent occurrence of high blood pressure in the absence of clinically significant changes in the kidneys and arteries. Since then the literature has become replete with numerous articles dealing with hypertension and vascular lesions of the kidneys under the following headings: arteriolar sclerosis, nephrosclerosis, essential benign and malignant hypertension, etc. Despite this voluminous literature relatively little is known of the etiology of the pathologic process involved or of the pathogenesis of hypertension in the various inflammatory lesions involving the smaller arteries of the kidney, except that renal ischemia may develop as a result of the obliterative changes in the walls of these vessels.

Crabtree and Chaset recently undertook to correlate hypertension and renal vessel changes in a series of 150 nephrectomies for severe unilateral renal lesions. They were unable to establish a sufficient correlation between the two above conditions, since the number of cases with hypertension (14 cases) were too few in comparison with the large number which showed renal vessel damage. After a careful study of 1,500 pathologic sections, they classified the kidneys on the basis of vascular changes in major portion of the kidney. In the entire group, 58 cases showed definite renal vessel changes. In the infectious group of 99 cases, which comprised 66 per cent of the total group, renal vessel changes were found in 46 cases (79 per cent). The incidence of renal vessel damage in the group of chronic pyelonephritis with hydronephrosis with or without nephrolithiasis was 49.3 per cent as compared with 42.8 per cent in chronic pyelonephritis with contraction. It is interesting to note that no alteration in the renal vessels was found in 3 cases with hypertension.

A. *Arteriosclerotic Kidney.*—Allbutt attempted to clarify the confused situation which attended the clinical group, "hypertension, kidney disease, arteriosclerosis," and proposed the following classification:

1. Hyperpiesia: cases in which high blood pressure dominated the clinical picture with little or no renal involvement
2. Bright's disease: in which true renal disease occurred with or without hypertension
3. Decrescent arteriosclerosis: in which the senile atheromas of the large arteries occurred, but not necessarily associated with high blood pressure or accompanied by any significant enlargement of the heart

The latter group must be differentiated from the arteriolosclerotic (or primary contracted or hypertensive) kidney which is accompanied by marked enlargement of the heart and a very high blood pressure. However, he failed to recognize or include cases of primary hypertension with renal insufficiency. The differentiation between primary hypertensive conditions existing with and without renal insufficiency and the recognition of pathologic criteria of two types of vascular renal disease corresponding to these two clinical forms were established by Volhard and Fahr. They considered only arteriosclerosis to be associated with simple or benign hypertension; whereas, a combination of atherosclerosis with inflammatory renal changes was believed to be responsible for the malignant form of hypertension (the so-called "*Kombinations Form*"). Subsequent contribution to the various phases of arterial and arteriolar changes were made by Herxheimer, Lohlein, Fahr, Volhard, and others.

It is generally agreed that a reciprocal relationship exists between hypertension and renal arteriosclerosis, but the question as to whether hypertension is the cause or the result of renal arteriosclerosis remains a moot one. Renal arteriosclerosis may involve the large and small arteries and arterioles, but in some cases the predominant changes occur in the arterioles, and in other cases in the larger interlobular arteries. Involvement of the arterioles alone is a rare phenomenon according to Kimmelstiel and Wilson. The preponderance of clinical and pathologic observations lends support to the view of Aschoff, Fahr, and Kimmelstiel that hypertension serves as an accelerating factor in the development of arteriosclerosis.

B. *Localized Arteriosclerotic Disease of the Renal Arteries.*—In the Harvey Lecture of 1938 Goldblatt stated that in a few cases of hypertension without arteriosclerosis, severe sclerosis and narrowing of the orifice or lumen of the main renal arteries or the larger extrarenal branches may occur and produce renal ischemia. Our knowledge of the relation of hypertension to localized arteriosclerotic changes in the renal arteries has been greatly enhanced by the contributions of Leiter, Blackman, Oppenheimer and associates, Stewart, and others. Leiter reported a case of chronic hypertension associated with arteriosclerotic occlusions of the main renal arteries, renal insufficiency, retinal arteriosclerosis, and contracted kidneys. Blackman studied the pathologic changes in the renal arteries in 50 cases of essential hypertension as compared with a control series of 50 nonhypertensive patients balanced as to age and sex incidence. Narrowing of the main renal arteries at or near the aorta was found in 86 per cent of the hypertensive subjects. The narrowing was quite pronounced (i.e., almost total occlusion in 54 per cent; of a less pronounced degree, i.e., constriction of lumen to 1.5 mm. or less in 32 per cent; and no significant constriction was observed in 14 per cent). On the other hand, appreciable narrowing of the main renal arteries was found in only 10 per cent of the control series.

Oppenheimer, Klemperer, and Moschkowitz observed hypertension in 15 (83 per cent) of 18 cases of unilateral narrowing of the renal artery and found arteriosclerosis and arteriolar sclerosis of the kidneys in each of the 15 cases. The relative frequency of hypertension was greater in this specific type of unilateral renal disease than in the two other types studied; viz., 32 per cent in unilateral hydronephrosis (with chronic pyelonephritis) and 23 per cent in unilateral congenital hypoplasia. They were of the opinion that the intrarenal arterial changes preceded the arteriosclerosis of the main renal arteries. Furthermore, arteriosclerosis of the aorta was present in 13 of the 15 cases with hypertension which compared favorably with the high incidence of hypertension (60 per cent) in 100 control cases of arteriosclerosis of the aorta.

Stewart recently described a case of severe hypertension in a 37-year-old male due to arteriosclerotic narrowing of the orifices of the renal arteries. The kidneys showed marked atrophy and histologic changes suggestive of chronic glomerular nephritis but no signs of arteriolar sclerosis. A fatal case of hypertension caused by a large localized arteriosclerotic plaque narrowing the orifice of the renal artery of a solitary acquired kidney in a 57-year-male was reported by Freeman and Hartley. The other kidney had been removed two years previously following a rupture and was histologically normal. Saphir and Ballinger recently reported 3 cases of severe arterial hypertension secondary to unilateral stenosis of the orifice of the renal artery with consequent ischemia of one kidney. In 2 of these cases autopsy revealed unilateral malignant nephrosclerosis in the contralateral kidney.

C. *Arteriolosclerosis of the Kidney.*—There is a unanimity of opinion concerning the fact that renal arteriolosclerosis is the cause of hypertension despite the fact that rare cases of renal arteriolosclerosis without hypertension have been reported by Lohlein, von Monakow, Fahr, and Kimmelstiel. The incidence of renal arteriolosclerosis in cases of cardiac hypertrophy with hypertension is very high; the figures vary: 90 per cent (Bell and Clawson), 97 per cent (Herxheimer and Schulz), and 100 per cent (Fishberg). Kimmelstiel and Wilson have pointed out that these figures are based on the quantitative estimation of arterial damage and hence are open to question. They maintained that less than 50 per cent of the cases show a completely diffuse arteriolosclerosis. They believed that Goldblatt's experiments may be considered as positive evidence in support of the contention that obstruction to kidney circulation is a primary factor in the production of hypertension.

Volhard and Fahr proposed a classification of hypertension based on the degree of arterial and arteriolar changes in the kidney. They designated as:

1. Essential Hypertension, cases in which renal vascular changes are absent.

2. Benign Nephrosclerosis, cases in which hypertension is secondary to arterial and arteriolar sclerosis.

3. Malignant Nephrosclerosis, cases characterized by specific arterial lesions in the kidney, namely productive endarteritis and necrotizing arteriolitis.

Later Fahr designated a subgroup of benign nephrosclerosis characterized by focal glomerulitis and elevated nonprotein nitrogen in the blood as a decompensated form of benign nephrosclerosis.

This classification appeared to be inadequate because of its failure (a) to reconcile the clinical and pathologic findings in the three groups, (b) to explain the borderline cases, and (c) to account for the characteristic arterial changes being present in other conditions; i.e., contracted pyelonephritis, diffuse glomerulonephritis, etc. The need for accurate histologic criteria consistent with the various clinical states and for a closer correlation between the degree of renal impairment and pathologic changes soon became apparent. As a result of an intensive clinical and pathologic study, Kimmelstiel and Wilson have proposed several modifications of this classification which have received popular recognition. They maintained that benign hypertension and benign nephrosclerosis may show a parallel development but in the early stages are not etiologically related and in the later stages exhibit a reciprocal relation. They believed that malignant hypertension and malignant nephrosclerosis show a definite correlation and considered malignant hypertension as a primary generalized vascular disease of which the malignant nephrosclerosis of Fahr represents the "renal end stage." They regarded endarteritis in its diffuse form as the most characteristic histologic sign of malignant hypertension. Arteriolitis (arteriolar necrosis) is more closely related to terminal renal failure than to hypertension per se. As the result of a study of the relation of periarteritis nodosa to malignant hypertension, they suggested that two factors are necessary for the development of malignant hypertension; namely, pre-existing hyperactivity or sensitivity of the arteries on which is superimposed a precipitating factor, allergic or otherwise.

Moritz recorded 3 cases with essential hypertension and renal arteriolar sclerosis in which the lesion was limited to one kidney. Weiss, Parker, and Robb described a case of unilateral bleeding in a 27-year-old male which was diagnosed preoperatively as a malignant tumor of the kidney. At operation, sixty-seven days before death, the kidney was removed and a diagnosis of malignant nephrosclerosis was made. A comparison of the sections of both kidneys showed a striking increase in the extent and severity of the productive endarteritis in the nonoperated kidney during this interval.

D. *Thrombosis and Embolism of Renal Arteries.*—Little is known of the role of thrombosis of the renal artery in the production of hypertension. Welty recently analyzed the clinical features of 11 cases of

renal artery thrombosis which is so frequently mistaken for an acute abdominal catastrophe. Hypertension was present in every case. It is likely that the hypertension may be of the transitory type in the early congestive stage of renal artery thrombosis or entirely absent when acute total suppression of urine results from the thrombosis. Hypertension may develop in the later stages of renal artery thrombosis or embolism when ischemic changes in the kidney develop subsequent to occlusion or canalization of the affected artery. The relation of hypertension to thrombosis and embolism of the renal artery will undoubtedly be clarified when more is known of the late or delayed effects of such vascular lesions upon the kidney.

Fishberg noted the development of a transitory hypertension associated with embolism of the renal artery in a patient admitted with a diagnosis of myocardial infarction. The blood pressure remained about 100/60 mm. for two weeks until the patient developed the classical picture of infarction of the left kidney when the blood pressure rose to 155/108 mm. The blood pressure remained at this high level for five days and then gradually declined to the previous level.

E. *Infarct of the Kidney.*—A review of the literature reveals a difference of opinion regarding the effect of renal infarct upon the production of hypertension. Experimental evidence fails to substantiate the claim that renal infarction due to multiple emboli gives rise to hypertension. This is confirmed by the negative results reported by Senator in 1911 following the injection of liquid paraffin into the renal arteries; by Cash in 1924 following injection of insoluble Berlin blue and by Apfelbach and Jensen in 1911 following injection of charcoal particles. The clinical evidence supporting this contention is likewise scant. Boyd and Lewis described an unusual case in which a large infarct of the right kidney was found during a bilateral exploratory operation for a questionable adrenal tumor in a man aged 31 years. Six months after right nephrectomy, the blood pressure had decreased from 200/120 mm. to 124/84 mm., but the changes in the eye grounds persisted. They believed that the arterial disease present in the right kidney was responsible for the hypertension and the infarct was of secondary importance. Young mentioned a similar case but gave no details. Hoxie and Coggin recently reviewed 205 cases of renal infarction and found the blood pressure to be above 140 systolic and 90 diastolic in 34 per cent of the patients but stated that in no instance could it be proved that the hypertension was due to the renal infarction.

Pathologic studies of infarcted kidneys not infrequently reveal arteriolar changes in the tissues adjacent to the infarcts which lends credence to the belief that antecedent or pre-existing arterial disease is the primary factor responsible for the hypertension in cases of renal infarct. The role of spasm in the production of the arteriolar changes as well as the infarct is discussed elsewhere. However, Russell demonstrated glomerulitis in the vicinity of acute renal infarcts. Klemperer

and Otani observed necrotizing arteriolitis in the periphery of aseptic renal infarcts and attributed these changes to ischemia. Kimmelstiel and Wilson found similar glomerular and arteriolar changes in the same location but believed that these changes were the result of the action of diffusible toxins produced by the breakdown of the kidney tissue. They suggested that toxic and ischemic factors may combine to produce the alterative glomerulitis present in these cases.

Oppenheimer and his associates observed two patients who developed hypertension after they presented symptoms of renal infarct. One case terminated fatally and at necropsy a very large anemic infarct was found in one kidney and a marked congestion in the other kidney.

F. *Spasm of the Renal Arteries.*—Although the role of spasm of the small arteries and arterioles in the development of hypertension has not been definitely established, it appears that the degree of renal ischemia resulting from angiospasm of the renal arteries and its influence upon the subsequent development of hypertension are dependent upon the size of the spastic vessel and the duration of the spasm. Total infarction of the kidney infers complete obstruction of the main renal artery and is accompanied by total arrest of secretion from the affected kidney. The acute pain which accompanies these cases at the onset is due to the sudden tension of the renal capsule as a result of the acute hyperemia of the kidney. Intermittent spasm of the smaller arteries and arterioles may lead to localized areas of ischemia as a result of partial infarction, but determination of the extent of functional impairment may be difficult or impossible.

Fahr was the first to suggest the etiologic role of spasm in the development of renal arteriolar changes. Bell and Pedersen offered the following interesting hypothesis: Hypertension begins as a spastic condition of the arterioles, which in certain organs, such as the kidney, may lead to arteriosclerosis; thus a vicious cycle is set up where one condition aggravates the other. If infection supervenes, the renal arterioles and glomeruli may be severely damaged, as a fulminating hypertension with uremia develops. Kimmelstiel and Wilson are of the opinion that spasm alone does not cause arteriolitis, as evidenced by the fact that this lesion is absent in Raynaud's disease and acute eclampsia. Klemperer and Otani suggested that the endarteritis in larger vessels may produce endarteritis in corresponding arterioles, thereby producing arteriolar necrosis. They are in accord with Volhard's conception that a constitutional or acquired angiospastic factor plays a determining role in the development of the endarteritic process. Prinzmetal and Wilson have shown that the vasospastic process in malignant hypertension is universally distributed.

Volhard distinquished a specific angiospastic group of hypertensive cases in which the hypertension is not "renally conditioned": lead poisoning of the kidney and the kidney of toxemia of pregnancy. He

maintained that the changes which occur in the kidney of toxemia of pregnancy are due to toxic substances of extrarenal origin which cause excessive vascular spasm, resulting in some cases in typical endarteritic changes in the vessels of the kidney and ultimately hypertension. The tubular changes in such a kidney are considered part of a general vasoconstriction.

Some writers, particularly the Germans, attach particular significance to the role of angiospasm in pathogenesis of various vascular disturbances; i.e., cerebral apoplexy, renal infarction, embolism, etc. Recent investigations on the pathologic substratum of renal infarcts tend to prove that an antecedent circulatory disturbance such as embolism is not an absolute prerequisite in the development of renal infarct. According to Fahr a toxic spasm of the renal vessels of sufficient duration may lead to degenerative changes in the parenchyma varying from a localized area of ischemia to total cortical necrosis. On the basis of clinical and experimental investigations, Westphal maintained that a state of angiospastic ischemia may precede any apoplectic lesion and that in the kidney a temporary or brief ischemia may result from contraction of the larger renal arteries and induce bloody extravasation in the form of a hemorrhagic infarct. In 1927 Neuberger reported a series of renal infarcts without demonstrable embolism and attributed their development to the occurrence of parenchymatous lesions resulting from mild or transitory disturbances of the renal vessels. Jaffe was of the opinion that vascular spasm was responsible for the rare cases of renal and splenic infarcts in which changes in the walls of the arteries and veins cannot be demonstrated and the foramen ovale is closed. Weiss likewise reported a case of renal infarction occurring twelve days after an apoplectic stroke and accompanied by transitory speech disturbance and rapid subsidence of the paresis. He attributed both vascular lesions to an angiospastic involvement of the blood vessels.

G. *Primary Inflammatory and Obliterative Lesions of the Small Renal Arteries and Arterioles.*—A review of the literature reveals very little data or observations on the occurrence of hypertension in primary chronic inflammatory or obliterative disease of the small renal arteries and arterioles.

1. *Endarteritis Obliterans:* Volhard has stated that in rare instances primary endarteritis may serve as the cause of an angiopathic type of hypertension which is "renally conditioned." The very rare cases of granular kidney due to amyloidosis are another example of the angiopathic type of renal hypertension. The etiology of the various occlusive vascular lesions of the kidney is not clearly defined but appears to be of an infectious or toxic nature. The obliterative process may be the result of (a) the growth of tissue from or beneath the intima, (b) the organization of a thrombus, or (c) the formation of adhesions between the vessel wall and the surrounding tissues. At times it may be extremely difficult to differentiate one type of vascular lesion from the

others. The clinical and pathologic picture is further complicated by the fact that obliterative endarteritis occurs in other diseases and organs; i.e., chronic nephritis, tuberculosis, syphilis, tumors, etc. In view of the definite relation which has been established between hypertension and the obliterative arteriolar lesions of chronic pyelonephritis and arteriolosclerosis by recent clinicopathologic studies and experimental investigation, it is logical to assume that the obliterative lesions of these rare primary lesions of the smaller renal arteries may produce ischemic changes in the kidney and subsequently hypertension. We may look forward to seeing more frequent reports of hypertension associated with primary obliterative lesions of smaller renal arteries in the immediate future.

Volhard mentioned syphilitic endarteritis as one of the causes of hypertension. Fishberg stated that hypertension may occur in the rare cases of amyloid contracted kidney due to syphilis and conceivably in rare sclerogummatous form of renal syphilis. Rich noted hypertension in 12 of 19 cases of syphilitic nephritis.

2. *Thromboangiitis Obliterans of the Kidney:* Jaeger has described a visceral form of thromboangiitis obliterans in association with the typical vascular manifestations in the extremities. He demonstrated that the visceral lesions are characterized by thrombotic occlusion with organization and appear to involve the veins as well as the arteries. Leiter recently reported a unique case of acute hypertension, with normal renal function, due to thromboangiitis of the smaller renal arteries in a tabetic patient.

3. *Periarteritis Nodosa:* Periarteritis nodosa is a relatively uncommon vascular disease whose pathologic features were first described by Rokitansky in 1852 and whose clinical aspects were correlated by Kussmaul and Maier in 1866. The characteristic symptoms of this disease are fever, anemia, polymyositis, polyneuritis, gastrointestinal disturbances, renal lesion simulating nephritis, retinal arterial changes, cerebral manifestation simulating encephalitis, and hypertension. These symptoms are due to the widespread necrotizing and obliterating vascular lesions. The disease is of unknown etiology, but the nature and diffuseness of the lesions suggest an infectious background. The chief pathologic change is a patchy destruction of the media of the small arteries. Aneurysmal dilatations may develop in the weakened walls of the vessels, usually at the base of a branching vessel. The lumen of the vessels is frequently narrowed or obliterated by the scars.

The frequent involvement of the kidney in this disease was first emphasized by Gruber who found renal changes in 74 per cent of the 108 collected cases and later by Arkin who found renal changes in 80 per cent. The usual signs and symptoms of a renal lesion in this disease are strongly suggestive of a nephritis which accounts for the frequent incorrect clinical diagnosis of "hemorrhagic nephritis." In several cases the erroneous diagnosis of an "acute surgical kidney" (i.e., peri-

nephritic abscess, calculus, pyonephrosis, neoplasm, etc.) was made and exploratory operation performed, the true diagnosis being made at necropsy. Wever and Perry reported a case in which death followed an operation for perirenal hemorrhage and collected 8 cases in which death was due to renal or perirenal hemorrhage.

Bernstein found that hypertension was present in the majority of cases where the blood pressure was recorded. Spiegel observed hypertension in 9 of 15 cases. It is surprising that the incidence of hypertension is not greater in view of the generalized nature of the disease and the degree of vascular resistance offered by such an extensive disease process. It is difficult to evaluate the role of renal ischemia in the development of hypertension for, unfortunately, no data are available on the incidence of hypertension in cases with or without demonstrable renal changes. However, a review of literature reveals that hypertension is an almost constant finding in cases with renal changes.

H. *Traumatic Injuries of the Kidney.*—There is little information available concerning the role of traumatic injuries of the kidney in the pathogenesis of hypertension. Too frequently the attending surgeon or urologist focuses his entire attention on the immediate condition following the rupture and fails to consider the late sequelae of traumatic injuries of the kidney. In the minor or least serious types of renal trauma, such as contusions or small cortical, capsular or perinephritic tears accompanied by slight intrarenal or extrarenal hemorrhage, repair of the wound is initiated early and progresses at a rapid rate, being fairly advanced after one week and the ultimate effect on the kidney function is scarcely detectable. However, in the more serious types of renal injuries, such as parenchymal tears, fragmentation and rupture of the vascular pedicle accompanied by extensive hemorrhage in and around the kidney or by extravasation of urine, the degree of renal damage and dysfunction is commensurate with the amount of kidney tissue destroyed and the nature of the reparative process. Ordinarily connective tissue fills in the spaces between the torn edges of the wound, but in severe injuries a variety of pathologic changes may occur in and about the kidney long after the primary injury and lead to renal ischemia or serious impairment of renal function. Among these changes, which may appear singly or in combination, are included: fibrosis, necrosis, infection, hydronephrosis, calculi, cystic degeneration, calcification, thrombosis, infarction, constriction of blood supply, perinephritis due to hemorrhage, extravasation, or infection, etc. One cannot emphasize too strongly the value and importance of early surgical intervention in cases of extensive injuries to the kidney in order to prevent development of such degenerative lesions which may cause serious permanent or irreparable damage, impairment of renal function, and possibly hypertension. It must be borne in mind that surgical intervention does not always imply nephrectomy but may enable the surgeon

to control bleeding, repair the wound, and drain and conserve the traumatized kidney.

There are relatively few case reports of hypertension following injuries of kidney. The case of Freeman and Hartley has been previously mentioned. Nesbit and Ratliff reported a case of hypertension associated with sclerotic and cystic nephropathy (ischemic) resulting from trauma. The patient, a male aged 32 years, had sustained a fracture of the right kidney ten years previously and nine years later developed signs of malignant hypertension. Following nephrectomy there was a marked improvement for five months followed by a progressive increase in the blood pressure. Pathologic study disclosed a cyst and marked vascular changes in the capillaries, arterioles, and larger arteries. They maintained that if the hypertension resulted from the ischemic lesions of the injured kidney, its prolonged duration led to vascular changes in other parts of the body and rendered the condition beyond repair. Schroeder and Steele reported the occurrence of hypertension in a case in which the kidney was replaced by calcified cysts. The latter was classified as an obstructive lesion but in all probability belongs to the group of post-traumatic sequelae.

Braasch, Walters, and Hammer observed hypertension in 2 cases following severe renal injury which was attributed to nephrosclerosis. These authors have emphasized the role of operative trauma and infection as etiologic factors in hypertension. They reported 14 cases in which the blood pressure was normal prior to a conservative renal operation, but hypertension developed following operation. Each case presented evidence of reduced function and persistent infection following the conservative operation and after removal of the affected kidney the blood pressure returned to normal. Widespread tissue atrophy and vascular sclerosis were found in the removed kidneys. The conservative operations or underlying condition for which such operations were performed included nephrolithiasis, nephrostomy, ureterolithotomy, nephropexy, ureterovaginal and vesicovaginal fistulas. They also observed that hypertension developed following transplantation of the ureters into the sigmoid in 2 cases. Postoperative urographic examination revealed a functionless kidney on one side, and following the removal of the affected kidney, the blood pressure returned to normal.

An important observation made by these authors was that a postoperative increase in blood pressure occurred more frequently following conservative operations for renal and ureteral lithiasis than other lesions. Hence they stress the advisability of considering nephrectomy in the presence of renal stone and extensive infection in order to circumvent the possibility of subsequent development of sclerotic pyelonephritis with hypertension.

I recently observed a case of postoperative hypertension develop in a male patient, 52 years of age, with a left renal calculus and left

hydronephrosis and a preoperative blood pressure of 140/90. Following operation, which consisted of nephrolithotomy, a Foley plastic repair of the pelvis and a Deming nephropexy, the patient had a stormy convalescence complicated by a fecal fistula and acute pyelonephritis. Seven months later the patient had developed a hypertension of 180/110. Pyelography revealed a small well-healed pelvis with pyelonephritic changes in the calyces. Nephrectomy was advised but refused.

I. *Compression of Renal Vessels by Intrinsic or Extrinsic Lesions.*—

There are relatively few reports in the literature of hypertension associated with constriction of the renal arteries by intrinsic or extrinsic lesions of the renal arteries. Leadbetter and Burkland reported a case of marked hypertension (160 to 220 mm. systolic) of five years' duration in a 5½-year-old boy. The blood pressure returned to normal (96/70) following the removal of an ectopic kidney, whose main renal artery was nearly occluded by a smooth muscle tumor in the wall of the artery. Blatt and Page reported a case of hypertension in which the main renal arteries of both kidneys were constricted throughout their entire course by a retroperitoneal lymphosarcoma involving the kidneys, ureters, adrenals, abdominal aorta, and inferior vena cava. There was a moderate hydronephrosis in both kidneys due to constriction of both ureters. It appears that more than one factor may be responsible for the hypertension in each of the above cases. In the former, the anomalous position of the kidney was accompanied by abnormalities in the course, position, and size of renal vessels, which may have impaired the renal circulation and produced ischemia. In the latter, the bilateral hydronephrosis and evidences of an early glomerulonephritis were present.

Aneurysm of the renal artery is an extremely rare condition which may interfere with the renal circulation with resulting ischemic changes in the kidney. In an occasional case the aneurysm of the main renal artery may obstruct the outflow of urine, causing increased back pressure and hydronephrosis. Aneurysms of an intra- or extrarenal branch of the renal artery may produce pressure on one or more calyces, resulting in hydrocalicosis and even stone formation. Onel and Valencia observed a case of renal aneurysm in a patient with repeated gravidic nephropathies and persisting hypertension. Howard, Forbes, and Lipscomb recently reported a case of aneurysm of the left renal artery in a 5-year-old child with persistent hypertension successfully treated by nephrectomy.

J. *Miscellaneous Vascular Lesions.*—

1. *Thrombosis of Abdominal Aorta:* Hypertension has been recorded in a group of rare primary vascular lesions of the aorta which produce or are accompanied by secondary changes in the kidneys or the renal arteries. Thrombosis of the abdominal aorta is a rare but invariably fatal condition occurring in elderly people and is usually associated

with chronic cardiovascular disease or acute infection. Hypertension was a prominent feature in the majority of about 150 cases in the literature. Ronald and Leslie recently described a case in a 43-year-old male who had a hypertension of 260/140. At autopsy the thrombosis of the abdominal aorta was accompanied by two infarcts of the left kidney, complete thrombosis of the left renal artery and partial thrombosis of the right renal artery, and bilateral arteriosclerosis of the kidney.

2. *Coarctation of the Aorta:* Hypertension is also frequently observed in coarctation of the aorta. Rytand maintained that the elevation of blood pressure in patients with coarctation of the aorta is due to the action of pressure substances formed in ischemic kidneys as a result of interference with the blood supply of the kidney. The latter change is attributed to an increased resistance in the smaller vessels (arterioles) which receive blood from the aorta proximal to the stenosis at its isthmus. This is substantiated by animal (rat) experiments; viz., partial constriction of the aorta proximal to one or both renal arteries leads to hypertension, whereas the same type of constriction plus simultaneous bilateral nephrectomy does not result in hypertension.

3. *Aneurysm of the Aorta:* Hypertension has been reported in cases of saccular and dissecting aneurysms of the abdominal aorta and aortic arch. These pathologic lesions may cause serious impairment of the blood supply to the kidney, depending upon the point of origin and the size of the sac. Hamburger and Ferris observed high blood pressure in only 1 case in their series of 6 cases of dissecting aneurysms and commented upon the fact that while most observers consider high blood pressure to be a typical finding in this condition, they found the blood pressure to be normal or the patient to be in a state of peripheral circulatory collapse on admission. Buckley recently reported two cases of hematuria associated with dissecting aneurysms of the abdominal aorta. Hypertension was present in both cases. In 1 case rupture of the aneurysm had occurred and shock, hematuria, and fluctuating blood pressure were the cardinal symptoms.

IV. Neoplasms of the Kidney and Adrenals.—

A. *Kidney Tumor in Adults.* A review of the literature reveals relatively few references to the occurrence of hypertension in cases of renal or adrenal neoplasms. In 1898 Neusser was the first to emphasize the association of hypertension with hypernephromas, particularly of the adrenal gland. Subsequent contributions to this phase of the subject were made by Oppenheimer and Fishberg, Braasch and Griffin, and others. In their series of 101 cases of primary urinary tract pathology associated with hypertension, Maher and Wosika encountered only 2 cases of renal tumors.

Braasch and Griffin studied the blood pressures of 40 patients operated upon at the Mayo Clinic for renal neoplasm and found the blood pressures were within normal limits in 26 cases and increased in 14 cases.

In several cases the hypertension was present for several years prior to the onset of symptoms. They believed that the hypertension in these cases was of the essential type. Following the removal of the kidney tumor, the blood pressure remained stationary in most cases and showed a slight decrease in a comparatively few cases. In the same clinic Horton and Morlock compared the hypertension occurring in cases of hypernephroma with that in other types of renal tumor but failed to find an increased incidence in hypernephroma or any difference in postoperative reduction in blood pressure. A systolic blood pressure of more than 200 mm. of mercury was present in 4 patients who were living five years after operation. Based upon the above reports, Braasch and Griffin concluded that hypertension was of little prognostic significance in renal neoplasms.

Subsequently Braasch, Walters, and Hammer reported 38 instances of hypertension (27.7 per cent) in a series of 137 adenocarcinoma of the kidney, including hypernephroma. They attached much significance to the factor of age in explaining the high incidence of hypertension in this group, since 87 (63.5 per cent) of these patients were 50 years of age or more. The postoperative course of 43 patients operated upon for hypernephroma was carefully studied. Preoperative hypertension was present in 21 of these cases. Following operation the blood pressure returned to normal in 9 cases, was temporarily reduced but subsequently became elevated in 3 cases, and was uninfluenced in 9 cases.

Crabtree and Chaset reported 6 cases of hypernephroma with preoperative hypertension. Following nephrectomy there was a slight improvement in blood pressure in only 1 case. They observed that a higher degree of hypertension usually occurred in cases of hypernephroma as compared to other severe unilateral renal lesions and attributed this change to the age factor.

Neusser advanced the theory that hypertension in cases of hypernephroma was caused by the absorption of some secretion from the tumor cells of suprarenal origin. Braasch and Griffin pointed out that there are clinical evidences of other abnormalities in the vascular system; i.e., fever, increased pulse rate, and telangiectasis, which may be attributed to the absorption of some specific substance. These absorptive vascular phenomena are not to be confused with vascular changes resulting from mechanical obstruction of the venous circulation by the tumor; i.e., varices of the abdominal wall and legs, left-sided varicocele. There are conflicting reports concerning the results obtained by chemical examination of renal tumor tissue for adrenal cortical elements which might be responsible for the hypertension as well as other symptoms; i.e., fever, pigmentation of skin, and changes in blood volume. In 1931 Rowntree, Greene, Swingle, and Pfiffner made biologic assays of hypernephroid tumors and found the cortical hormone (adrenal cortex extract) to be comparable in amount to that present in the normal adrenal cortex. In 1932 Kendall failed to find any evidence of

adrenal secretion in two tumors and obtained similar results in a subsequent examination of three other renal adenocarcinomas, employing his new chemical method for determining the amount of adrenal cortex secretion.

Dean found that hypertension occurred in practically every one of a small group (approximately 10 cases) of papillary tumors of the kidney pelvis and ureter in which obstruction, infection, and destruction of the renal parenchyma were marked. There was no reduction in the hypertension following operation.

Braasch, Walters, and Hammer observed hypertension in 6 cases of epithelioma of the renal pelvis, and following nephrectomy, the blood pressure returned to normal in only 1 case.

It is surprising to note that little or no reference was made in any of the above articles to the possible role of ischemia in the production of hypertension in cases of renal neoplasms. Obviously, varying degrees of renal ischemia may occur as a result of vascular changes produced within the kidney by the tumor. These changes may manifest themselves in any of the following ways: (a) compression of the blood vessels in the renal parenchyma adjacent to the tumor; (b) compression of the vascular pedicle by the tumor; (c) compression, distortion, or angulation of the vascular pedicle by the displaced kidney; (d) vascular changes in the parenchyma induced by infiltrating tumor tissue; (e) thrombosis of the large or small renal vessels of one or both kidneys due to infiltration by tumor cells or to stasis. Undoubtedly future studies of renal tumors will throw some light on the relation of the pathologic features of the tumor to hypertension.

There are no data available at present to suggest any relation between hypertension and the development of recurrences or metastases from primary renal carcinomas, including hypernephroid tumors in adults or secondary metastatic nodules in the kidney from neoplasms elsewhere in the body. However, there are some data on hand concerning the relation of hypertension to recurrences and metastases in Wilms' tumors. In 1938 Bradley and Pincoffs reported 5 consecutive cases of Wilms' tumor accompanied by hypertension and observed that in 2 cases the blood pressure decreased following nephrectomy but rose again after recurrence of the tumor.

CASE 14.—(G. U., No. 896.) W. T., 52 years of age, white, male, married, business executive, was admitted to the Sinai Hospital on Mar. 21, 1930, complaining of hematuria. The patient had been in good health until four years before when he had passed blood for the first time. Hematuria recurred six months and again six days before admission. There were no other urinary symptoms present.

Abdominal examination revealed a palpable, but not tender, right kidney. Examination of the urine revealed a faint trace of albumin and many red blood cells, and a moderate number of pus cells. His blood urea was 39.55 mg. per cent. On cystoscopy blood was seen escaping from the right ureteral orifice. Pyelogram revealed compression and elongation and partial obliteration of the lower and middle major and minor calyces. A diagnosis of renal neoplasm was made.

On Mar. 22, 1930, a right nephrectomy was performed and a tumor was found in the lower pole of the right kidney. The patient made an uneventful recovery and was discharged from the hospital on Apr. 8, 1930.

His blood pressure varied between 180 and 184 systolic and 110 to 112 diastolic prior to operation. At the time of discharge from the hospital, his blood pressure had fallen to 154/82. The patient was followed by his family physician for five years. For the first three years after operation his general health was excellent and his blood pressure did not exceed 156/84, but in the next two years his blood pressure became elevated. The patient died five years after operation of cerebral hemorrhage.

The pathologic diagnosis was (1) chronic pyelonephritis, (2) chronic parenchymatous nephritis, and (3) hypernephroma with hemorrhagic extravasation and necrosis. The vascular changes throughout the renal parenchyma were relatively mild (grade 1+).

CASE 15.—(G. U., No. 1341.) A. W., white, male, 62 years of age, married, merchant, was admitted to the Sinai Hospital on Feb. 6, 1933, complaining of hematuria. His mother had died at the age of 65 years of carcinoma of the stomach. The patient was in good health until two years previously, when he developed intermittent pain in the left kidney region, accompanied by hematuria lasting three to four days. There were no urinary or general constitutional symptoms. About one year before admission he had hematuria which lasted for two days and was unaccompanied by other symptoms. He had hematuria again ten days before admission. He had lost seven pounds in the past year. Two days before admission he had had a recurrence of pain in the kidney region which was present at the time of admission.

Examination revealed slight tenderness over the left kidney. Neither kidney was palpable. Blood urea was 27.56 mg. per cent. Intravenous phthalein was 33 per cent for the first hour and 20 per cent for the second hour. Urine was negative except for 8 to 10 red blood cells and an occasional pus cell on microscopic examination. Cystoscopy and pyelography revealed a normal kidney pelvis on the right, but on the left there were compression and distortion of the upper and middle major calyces, suggestive of a renal neoplasm.

On Feb. 7, 1933, a left nephrectomy was done under ether anesthesia. The kidney contained a tumor measuring 3 cm. in diameter which compressed and distorted the middle major and upper major calyces of the left kidney. A calculus about the size of a lima bean was found in the middle major calyx. The patient made an uneventful recovery and was discharged from the hospital on Feb. 21, 1933. Upon admission to the hospital, the patient's blood pressure was 168/86; upon discharge the patient's blood pressure had fallen to 140/80. Subsequent blood pressure determinations were made by his family physician who stated that during the period of observation for one year following operation, his blood pressure did not rise above 144/80.

The pathologic diagnosis was adenocarcinoma of the kidney (papillary type). The tumor tissue showed extensive hemorrhagic extravasation with some necrosis. In the kidney tissue adjacent to the tumor, the tubules and glomeruli were atrophic and necrotic. The remainder of the kidney presented evidences of degenerative changes varying from cloudy swelling to actual necrosis of tubules and glomeruli with moderate fibrotic changes in the walls of the smaller blood vessels (grade 1+).

CASE 16.—(G. U., No. 1232.5.) J. S., 63 years of age, white, male, married, tailor, was admitted to the Sinai Hospital on June 11, 1932, complaining of pain in the lower left quadrant, vertigo, and dizzy spells. The patient had been in

the hospital about eight months previously for treatment of diabetes mellitus. The patient was put on dietary treatment with insulin, but he failed to carry out this regime carefully. He had lost considerable weight and was extremely weak. The patient also complained of diurnal frequency and nocturia with occasional dysuria. About five months before, he had had hematuria which recurred on the afternoon prior to admission.

Physical examination revealed the patient to be thin and emaciated. Neither kidney was palpable, but tenderness was present in the left upper and lower quadrants. Cardiac hypertrophy was present. The blood pressure was 220/110. Ophthalmoscopic examination showed fairly well advanced hypertensive changes. Urine showed 4+ sugar and many red blood cells. Blood urea was 38.35 mg. per cent; blood sugar was 244 mg. per cent. Cystoscopy and pyelography were performed and a diagnosis of left renal neoplasm (hypernephroma) was made. X-ray studies of the chest and long bones failed to reveal any evidences of metastasis. The patient's diabetic condition was regulated by dietary regime and insulin therapy. On July 1, 1932, a left nephrectomy was performed under spinal anesthesia. The patient made an uneventful recovery and was discharged from the hospital on Aug. 18, 1932.

Following his operation, the blood pressure gradually fell and remained at 162/88. The patient returned to his family physician for observation and treatment of his diabetic condition. For the next eight months his blood pressure remained stationary at the above level. About July, 1933, the patient died suddenly of cardiac failure.

The pathologic specimen showed a large, irregular nodular tumor occupying the upper two-thirds of the kidney. The tumor was only partly encapsulated and in several areas appeared to infiltrate the surrounding kidney tissue. The vascular pedicle contained no tumor infiltration. Histologic study revealed an alveolar type of hypernephroma. Acute and chronic inflammatory changes were found in the presumably normal kidney tissue and the blood vessels in the same area showed only scant changes (grade 1+).

B. *Kidney Tumors in the Young.*—Daniel has recently made a comprehensive study of the hypertensive factor in 18 cases of Wilms' tumor in children between the ages of 8 months and 9 years. For children of this age period he considered a systolic blood pressure below 10 mm. of mercury as normal, 110 to 125 mm. as moderately elevated, and above 125 mm. as extreme elevation. Using these criteria, he found 4 cases with normal blood pressure, 6 with moderate elevation, and 8 with extreme elevation. Braasch, Walters, and Hammer observed definite hypertension in 5 of 18 cases of Wilms' tumor. One may infer from these findings that hypertension is a frequent but not constant finding in cases of Wilms' tumor.

Koons and Ruch recently reported a case of hypertension in a 7-year-old girl with a Wilms' tumor of the left kidney relieved by nephrectomy. The preoperative blood pressure was 190/155 and on the eleventh postoperative day was 116/76. Subsequent postoperative findings were unfortunately not recorded.

Daniel maintained that the hypertension of these cases was the result of renal ischemia, produced mechanically by the tumor, thus differing from Bradley and Pincoffs who attributed the elevated blood pressure

not to interference with the renal blood supply but to the fact that the tumor tissue, like renal tissue, possessed the property of causing an elevation in blood pressure when altered by certain types of damage. Koons and Ruch likewise attributed the hypertension to interference with renal circulation by invading tumor tissue at the renal pedicle. They also suggested that the neoplastic mass surrounding the kidney may act in the same manner as the cellophane envelopes used by Page to produce experimental hypertension. Daniel observed a striking reduction in blood pressure following irradiation in 3 cases with extreme hypertension, and following nephrectomy the blood pressure remained at normal levels. The beneficial effect of irradiation was thought to be due to a reduction in the size of the tumor mass and the consequent lessening in the amount of ischemia. He found that when the hypertension was of sufficient duration to have allowed the development of sclerotic changes in the arterioles of the presumably good kidney, neither irradiation nor nephrectomy had a beneficial effect upon the hypertension.

Daniel explained the hypertension associated with local recurrence in the 2 cases of Bradley and Pincoffs and in 1 personal case on the basis of renal ischemia resulting from tumor growth about the vascular pedicle of the remaining kidney. Furthermore he found that the predominant cell type of Wilms' tumor, epitheloid, mesoblastic or mixed, had no influence upon the presence or absence or hypertension. He concluded that hypertension in cases of Wilms' tumor is of grave prognostic significance and is probably indicative of tumor growth in the region of the vascular pedicle.

C. *Adrenal Tumors.*—Tumors of the adrenal gland have recently become the subject of renewed interest and much study on the part of pathologists, clinicians, and surgeons. For practical purposes they may be classified into two main groups: (1) adrenal cortical tumors, derived from the mesoderm of the wolffian body, and (2) adrenal medullary tumors, originating in structures giving rise to the sympathetic nervous system. The most common tumor of the adrenal is a hyperplasia of the cortex which has a tendency to produce changes in the sexual characteristics of the affected person (the so-called "*syndrome génito-surrénal*" of Gallais or "adrenal hirsutism" of Krabbe).

The earliest reference to the occurrence of hypertension in cases of adrenal tumors was made by Neusser, in 1898. He reported 2 cases in which the clinical course was typical of nephritis, but at necropsy an adrenal neoplasm (carcinoma) was found and the kidneys and arterioles appeared to be normal. In a comprehensive review of the literature by Oppenheimer and Fishberg in 1924, only 15 cases of chronic nonnephritic hypertension associated with adrenal tumors were collected; 11 cases were cortical tumors and 4, medullary (paragangliomas). In 1938 Nuzum and Dalton collected 29 cases of hypertension ascribed to hyperplasia or tumor of the adrenal cortex and added 1

personal case. The pathologic findings were: carcinoma, 13; cortical adenoma, 4; hyperplasia, 8; tumor (type not stated), 3; no pathologic data, 2.

According to these authors, hypertension is a frequent finding in cases of diffuse or circumscribed (adenomatous) hyperplasia of the adrenal cortex. This is substantiated by the studies of Aubertin and Ambard who studied 8 cases of hypertension and found diffuse cortical hyperplasia in 4, cortical adenomas in 3, and normal gland in 1. One of the above authors found cortical adenoma in 5 cases in a series of 35 cases of hypertension as compared to 1 case of cortical adenoma in 50 consecutive necropsies on nonhypertensive subjects. Volhard described 2 unusual cases in which the clinical picture was that of diffuse nephritis with hypertension and albuminuria and in each instance the hypertension disappeared following the operative removal of a hypernephroma of the adrenal cortex.

Tumors of the medullary portion of the adrenal gland are encountered less frequently than the cortical tumors and may be classified in two groups: benign and malignant. The benign tumors are derived from the formative cells of the sympathetic ganglions according to Oppenheimer and Fishberg and are divided into 3 types: (1) sympathoblastoma, composed of immature sympathoblasts; and (2) ganglioneuroma, composed of relative mature sympathetic cells and more differentiated than Group I; and (3) paraganglioma (or pheochromocytoma) composed of mature chromaffin cells. The malignant tumors are considered under the heading of neuroblastoma (or neurocytoma) and are usually diagnosed after early extensive metastases have occurred in skull, orbit, and long bones in children (Hutchinson type) and in the liver and lungs in adults (Pepper type).

Hypertension is rarely observed in cases of ganglioneuroma, neuroblastoma, and metastatic tumors of the adrenal but is an almost constant concomitant of paraganglioma. The clinical features of paraganglioma, which were first emphasized by Labbe and his associates, in 1922, are characterized by attacks of paroxysmal hypertension accompanied by other vasomotor phenomena; viz., headache, pallor, flushing, tachycardia, sweating, nervous apprehension, dyspnea, etc. This symptom complex is frequently referred to as the "suprarenal sympathetic syndrome" (Belt and Powell) and is caused by the hyperfunctioning adrenal tumor. The paroxysms of hypertension may be precipitated by undue physical or mental exertion and experimentally by the "cold pressor test."

When the presence of the tumor passes unrecognized for months or years, the attacks of paroxysmal hypertension increase in severity and frequency and permanent vascular and renal changes develop. The blood pressure remains high and paroxysmal attacks are superimposed. Cardiac hypertrophy, arteriosclerosis, retinal changes, and evidences of

renal damage appear. Patients with paragangliomas are extremely poor surgical risks and not infrequently exhibit a tendency to sudden death following a major or minor surgical procedure. In the latter cases, the cause of death is determined only by the finding of an adrenal medullary tumor at necropsy. I recently performed a bilateral exploratory of the adrenal glands in a case of paroxysmal hypertension but failed to find any pathologic changes in or about the adrenal glands.

In 1938 MacKenzie and McEachern collected 20 operative cases of paraganglioma from the literature. Walters and Kepler reported 4 cases of paraganglioma from the Mayo Clinic; 3 of these cases, which include the cases previously reported by Mayo and Walters, were successfully operated upon and no further paroxysms of hypertension have occurred; the fourth case was diagnosed at autopsy. Similar good results were obtained by Shipley, the Porters, MacKenzie and McEachern, and others.

In 1938, Nuzum and Dalton stated that approximately 85 cases of pheochromocytoma have been reported in the literature and added 1 case successfully treated by operation. A clinical diagnosis was made in only 20 cases. Blood pressure was not recorded in 36 cases and was said to be normal in 3 cases. In the group of 41 cases in which hypertension was found, the paroxysmal type was observed in 22 and the constant type in 19; evidence of kidney change was present in 3 cases of which 2 were atherosclerosis.

Hypertension has been observed in association with other adrenal conditions. Ferrara reported a case associated with a hematic cyst of the left adrenal. Demole and Rutishauser described a case of paroxysmal hypertension due to adrenal tuberculosis.

Oppenheimer and Fishberg maintained that there is no evidence based on experimental studies or chemical and pharmacologic examination of the blood to support the theory of Vaquez that the hypertension in cases of adrenal tumors is caused by a hyperepinephremia. The presence of large amounts of epinephrine in the tumor tissue, as demonstrated by microchemical and biologic methods, has been reported by Orth, Belt, and Powell, and others. The exact mechanism responsible for production of hypertension in cases of adrenal tumors has not definitely been established but in all probability is intimately associated with vascular changes produced in kidney and other parts of the body by the absorption of the increased epinephrine present in the tumors. Confirmatory evidence of this view is found in the relatively high incidence of arteriolosclerosis and arteriosclerosis in cases of paragangliomas and the frequent occurrence of diffuse hyperplasia and circumscribed adenomas in the adrenal cortex in patients with hypertension.

V. Congenital Anomalies of the Urinary Tract.—The relation of hypertension to congenital anomalies of the urinary tract, especially of the kidneys, must remain unsettled until more clinical observations and pathologic data are recorded. It is only within recent years that we

have gained a clearer understanding of the anatomic and clinico-pathologic problems arising from the diverse types of congenital malformation in the urinary tract and the complexity of the development of the permanent kidneys. Excellent classifications of the anomalies of the urinary tract have been proposed by Young, Hinman, Gutierrez, and others and a further discussion of same is intentionally omitted.

A. *Anomalies of the Kidney.*—Suffice it to say that practically every congenital malformation in the urinary tract, sooner or later, exerts some deleterious effect upon the integrity and function of the kidneys. Congenital malformations in the lower urinary tract may be responsible for a variety of pathologic changes in one or both kidneys, the most common change being hydronephrotic atrophy secondary to obstructive defects.

The literature abounds with numerous reports which confirm the fact that every congenital anomaly of the kidney proper, its excretory apparatus or its vascular supply, is a potential clinicopathologic entity. Some anomalies of the kidney exhibit a greater tendency to secondary changes than others. This is particularly true of anomalies of form (fusion types), of position (ectopic kidney), and of structure (aplastic, hypoplastic, and cystic kidneys). The intrinsic kidney lesion may manifest itself either as (1) extensive histologic changes (i.e., embryonic, sclerotic, or calcified glomeruli and tubules which occur in aplastic or hypoplastic kidneys as a result of defective development of the fetal kidney or cystic degeneration in polycystic kidney); or (2) hydronephrotic atrophy secondary to congenital obstructive lesions in the upper or lower urinary tract; or (3) renal atrophy secondary to anomalous blood supply; or (4) various types of inflammatory lesions of the parenchyma due to acquired infections; or (5) calculosis secondary to obstruction or infection. The secondary changes within the anomalous kidney may be so extensive as to impair seriously or to destroy totally the renal function. Not infrequently the opposite and presumably normal kidney shows signs of impaired function due to the additional strain imposed upon it by injured anomalous mate. It is highly probable and indeed possible that the secondary changes within the anomalous kidneys lead to varying degrees of renal ischemia and subsequently hypertension with greater frequency than is generally recognized at present.

The probability of hypertension associated with congenital anomalies assumes greater clinical significance when one considers that 40 per cent of pathologic conditions of the kidney and ureter are due to congenital anomalies of the kidney according to Gutierrez. In a series of 282 cases of hydronephrosis in infants and children, Campbell found the condition was secondary to an upper urinary tract anomaly in 193 cases (68.8 per cent) and in 508 cases of persistent pyuria in young children he found a total of 206 anomalies of the upper urinary tract in 179 patients (30 per cent).

Volhard regarded congenital hypoplasia of the kidney as a frequent cause of hypertension. Leiter has emphasized the fact that hypertension appeared to be a characteristic feature in cases of unilateral hypoplasia and allied developmental anomalies of the kidney even in the absence of severe renal insufficiency. He also called attention to the following striking but paradoxical situation; viz., the absence of hypertension in about 75 per cent of cases of renal dwarfism and rickets, diseases observed in children and associated with congenital dilatation of the urinary tract, and severe fibrotic atrophy of the kidneys.

In the case reported by Leadbetter and Burkland, the affected kidney, responsible for the hypertension, was situated in the pelvis, causing constriction and narrowing of the renal vessels in addition to partial occlusion of the main artery by a piece of abberant muscle. Removal of this kidney resulted in a cure. Leiter reported a nonoperative case of hypertension associated with congenital asymmetrical atrophy. Kerr described a case of severe hypertension in a young lady whose blood pressure returned to normal following the removal of a nonfunctioning embryonic (congenital hypoplastic) kidney weighing 19 Gm. Schroeder and Fish's case of hypoplasia associated with chronic pyelonephritis and arterial hypertension, which was successfully treated by nephrectomy, has been mentioned previously. Elsewhere in this paper I have called attention to the findings of Oppenheimer, Klemperer, and Moschkowitz who observed hypertension in 3 cases (23 per cent) in a series of 13 cases of unilateral congenital hypoplasia. Braasch, Walters, and Hammer found that in contrast to the high incidence of hypertension in cases of atrophic pyelonephritis, the blood pressure was normal in 5 operative cases of congenital hypoplasia.

In my series of 167 cases, neither preoperative nor postoperative hypertension was present in any of the congenital anomalous kidneys removed; viz., congenital ectopic kidney, 3 cases; double kidney, 1 case; congenital hypoplastic kidney, 1 case; horseshoe kidney (calculous pyonephrosis of one-half), 1 case. I have encountered an interesting case of hypertension (216/148) with advanced hypertensive changes in both fundi in a male, 50 years of age, who had been treated for chronic bilateral pyelonephritis for several years. A double kidney with complete duplication of both ureters was present on the right side; the upper rudimentary segment was the seat of a nonfunctioning chronic atrophic pyelonephritis. After much deliberation and with no promise of any cure or prolonged relief of hypertension, the ureter leading to this rudimentary ureter was ligated extraperitoneally rather than risk a hazardous heminephrectomy. For three months following operation, there was a slight temporary reduction in the blood pressure which varied between 180/120 and 194/140, but this was followed by a gradual return to the preoperative level in the next three months.

B. *Anomalies in the Blood Supply of the Kidney.*—There is a decided paucity of information concerning the relation of abnormalities in the

blood supply of the kidney and hypertension, particularly in cases of congenital malformations of the kidney. That such a relation may and does exist appears to be more than mere conjecture in the light of our increasing knowledge of the anatomic relations and pathologic effects of abnormal vascularization of the kidney. Anomalous renal arteries are an almost constant finding in congenital malformations of the kidney, the more pronounced the renal anomaly, the greater the variation of the blood supply. As a rule, anomalies of the renal arteries are accompanied by similar changes in venous system.

The possibilities for variations in the blood supply of the kidney are greatly due to (a) numerous peculiarities of the growth and development of the mesonephros, (b) the development of the renal vessels from the periaortic plexus which in turn originate from different embryonic arteries, (c) the vascularization of the kidney during its upward migration in the body, (d) other mechanical factors; i.e., influence of disturbances in body growth, pressure of adjacent organs, displacement by embryonic tumors, etc. Anomalous position of the kidney is one of the most important factors in the production of abnormalities in the blood supply of the kidney, for in the congenital abnormally situated kidney the blood supply arises from the nearest arterial source, and variations in the size, number, and course of the main arteries and the accessory branches are always found. The role of accessory or aberrant vessels in the production of hydronephrosis by virtue of compression of the ureter or pelvis is well recognized by urologists. This is well illustrated by Morton's case of hydronephrosis caused by an aberrant vessel and accompanied by hypertension.

It is highly probable that a direct relation exists between renal ischemia and anomalous renal vessels in some cases. Some authors maintain that the anemia from a defective arterial supply may be the important factor in the development of such renal anomalies of structure as the aplastic and hypoplastic kidneys. The evidence offered in support of this theory is based on the presence of following histologic changes within the aplastic or hypoplastic kidney; viz., sclerotic or calcified glomeruli and tubules, necrotic or functionless nephrogenic elements, varying degrees of fibrosis, or even complete absence of nephrogenic elements. Clinically these kidneys show extreme gradations of impaired renal function which may be conceivably followed by hypertension in many instances.

Varying degrees of renal ischemia may result from compression, elongation, or distortion of vascular supply of a normal or anomalous kidney by a variety of intrarenal and extrarenal lesions. For example, a congenital or acquired ptosis of the kidney or a dilated pelvis of a dynamic or mechanical nature may cause elongation and compression of the blood vessels. Likewise compression of the vascular pedicle may be caused by extrarenal and intrarenal neoplasms or metastatic nodules in the juxta-aortic lymph nodes.

C. *Congenital Polycystic Disease of the Kidney.*—The association of hypertension with polycystic disease of the kidneys is now well known to clinicians and urologists. Braasch was the first to call attention to the frequent occurrence of hypertension in this condition in 1916. Since then other writers, including Bell and Clawson, Braasch and Schacht, Hausman, Fishberg, Hawthorne and Rauscher, Albrittain and Cornbrooks, and Fahr, have commented on the frequency of persistent hypertension in these cases.

A review of the literature disclosed the fact that the opinion of Bell and Clawson, namely, persistent hypertension is not a frequent concomitant of congenital polycystic disease, is often quoted but rarely substantiated. To a nonbiased observer, it appears that their contention was based on insufficient data; i.e., the presence of a normal blood pressure in 4 of 8 cases of polycystic disease in which blood pressure determinations were made and the occurrence of cardiac hypertrophy in only 1 case.

Braasch and Schacht have presented very interesting statistics on the incidence of hypertension in polycystic disease. In a series of 190 patients whose average age was 43 years the systolic blood pressure exceeded 145 mm. of Hg in 61 per cent of the cases, and the diastolic pressure was more than 90 mm. of Hg in 55 per cent, and more than 95 mm. in 47 per cent. Elevated systolic blood pressures of 145 mm. or more were found in 71 per cent of the 71 patients reported dead of the disease. In a control group of the same age and sex, composed of patients suffering from chronic pyelonephritis, elevated blood pressure was found in 26 per cent. In this same group the incidence of hypertension among patients less than 50 years of age was 17 per cent as compared with 52 per cent of the patients in the same age group who were reported dead of polycystic disease.

Hawthorne and Rauscher found hypertension in 45 per cent of their 33 cases; Albrittain and Cornbrooks observed hypertension in more than 50 per cent of their 25 cases. Fahr noted hypertension in 4 of 6 cases. Fishberg maintained that the incidence of hypertension in this disease is between 65 and 75 per cent. Maher and Wosika observed 2 cases of polycystic diseases in their series of 101 cases of primary urinary tract pathology associated with hypertension.

Braasch and Schacht attributed the hypertension in polycystic disease to a generalized vascular disturbance as attested by the high incidence of retinal sclerosis and the frequent finding of obliterative changes in the small arteries and arterioles of the kidney. This contention is corroborated by the work of Hinman and Morrison in 1924, and Ritter and Baehr in 1928 who studied the arterial tree of polycystic kidney by injections. The former investigators found that the circulatory changes in a polycystic kidney appear to be of a mechanical nature, involving chiefly the finer cortical vessels by displacement and compression. The larger vessels show but very little change. The circulation

of the entire kidney was of the fetal type which may be evidence of the embryonic origin of the disease. The latter investigators were the first to emphasize the decrease in the size of the small arteries and arterioles of the kidney and to point out the similarity between the clinical course of polycystic disease and that of malignant hypertension (arteriolar sclerosis) and chronic glomerular nephritis.

Ritter and Baehr described two distinct pathologic processes responsible for the changes in polycystic disease: (1) between the cysts areas of atrophic sclerosed parenchyma are found which are similar to the typical picture of a hydronephrotic contracted or a tubular contracted kidney and are the result of mechanical pressure; and (2) in the larger masses of parenchyma which are situated near the capsule of the kidney and proximal to the cysts, the pathologic changes consist of atrophic tubules, hyalinized glomeruli, dense connective tissue, and sclerotic changes in walls of the small arteries and arterioles and resemble the picture of a primary contracted kidney. In many instances the arteriolar and parenchymal changes, which may manifest themselves as early as the third decade and as late as the sixth decade, simulated those described by Fahr under the term of malignant sclerosis.

The clinical course of polycystic disease may closely resemble that of chronic glomerular nephritis and the true nature of the condition is frequently overlooked until an attack of hematuria, infection, pain, or a palpable mass directs the examiner's attention to the possibility of a nonnephritic lesion of the kidney. However, patients with polycystic disease experience greater longevity than do patients with nephritis despite the presence of serious impairment of renal function as demonstrated by marked retention of nitrogenous and nonnitrogenous products in the blood and consistency low excretion tests; i.e., phthalein, urea clearance, specific gravity, etc. The sequence of events is indistinguishable from that observed in patients with chronic nephritis or malignant sclerosis. Renal insufficiency, arterial hypertension, cardiac hypertrophy, and retinal sclerosis eventually ensue in most patients who live to adult life and azotemia or dry uremia usually terminates the clinical picture.

Bothe reported a case of hypertension associated with bilateral polycystic disease, more advanced on the left side, in an 8½-year-old girl. An acute pyelonephritis appeared to be the contributory factor in precipitating the hypertension which persisted after the infection subsided. The blood pressure rose from 128/86 to 145/115 during the four-month period of renal infection.

Braasch, Walters, and Hammer reported hypertension in a case of polycystic disease in which one kidney was functionless due to diffuse infection. Following nephrectomy the blood pressure returned to normal and remained so for one year. In another case, presenting a similar condition, the blood pressure was temporarily reduced following nephrectomy, but hypertension returned in a few months.

I have observed a case of hypertension (170/100) associated with early bilateral polycystic disease in a female, aged 32 years. The left kidney was the seat of a severe infection and was removed. During the period of convalescence the blood pressure fell to 118/78. Unfortunately the patient failed to return for further observation. Nephrectomy was performed in another case for a severe infection of one polycystic kidney which was unaccompanied by hypertension.

The following 2 cases, which are not included in Table III, illustrate hypertension associated with bilateral polycystic disease in which the more seriously damaged kidney has been treated palliatively by puncturing the cysts and establishing a nephrocutaneous fistula after the method of Goldstein. A temporary reduction in blood pressure level was obtained in both cases.

CASE 17.—(G. U., No. 4692.) L. R., white, female, 29 years of age, married, housewife, was admitted to the urologic ward of the Sinai Hospital on Jan. 26, 1932, complaining of severe headaches and pain in the lumbar regions and epigastrium. The family history was essentially negative. The patient had enjoyed good health until eight years previously when she sustained a cerebral concussion in an automobile accident. Following this accident, the patient began to complain of severe occipital and frontal headaches which have persisted to date. In 1928 she was told that the headaches were due to her tonsils which were removed without benefit. Subsequently she developed epigastric pain and discomfort after eating, dull persistent pain in the lumbar regions, accompanied by nausea but no vomiting. About one month before admission she developed urgency, diurnal and nocturnal frequency, and had a cystoscopic examination elsewhere following which she was told that she had a kidney ailment.

Examination revealed both kidneys to be palpable, the left being larger and more irregular in outline than the right. Ophthalmoscopic examination was negative. The urine had a specific gravity of 1.008, and was negative for albumin, for sugar, and microscopically. The blood urea was 28.76 mg. per cent. Phthalein test was 55 per cent for the first hour and 10 per cent for the second hour.

Cystoscopy and pyelography revealed a bilateral congenital polycystic disease of the kidney. A fractional phthalein showed the right kidney to excrete 12.5 per cent in fifteen minutes as compared to 20 per cent on the left. Because the right kidney appeared to be more extensively involved, it was decided to puncture the cysts in this kidney first. On Feb. 2, 1932, the right kidney was exposed through a lumbar incision under spinal anesthesia and many cysts were punctured (Rosving's operation). The patient made an uneventful recovery and was discharged from the hospital on Feb. 28, 1932. Prior to this operation, her blood pressure was 160/96; following operation it fell to 140/92.

The patient was followed in the outpatient department. Three years later she developed marked suprapubic discomfort and menstrual disturbances which were caused by a fibroid tumor of the uterus, and a hysterectomy was performed. In the past few months before readmission, the patient complained of occasional sticking pain in the left kidney region accompanied by a sensation of distention in the same area. She also complained of nausea, eructation, and constipation. In the last two weeks before readmission, her headaches returned in a more severe form. She had no urinary symptoms other than occasional nocturia. She also complained of dyspnea and occasional edema of her ankles and eyelids. She was readmitted to the hospital again on April 26, 1938.

At this time examination revealed the left kidney to be enlarged and tender. The surface of the left kidney was nodular and irregular and several large cystic masses could be easily mapped out. The right kidney was not palpable. Ophthalmoscopic examination disclosed narrowing of the arterioles, increased light streaking, and A-V nicking in both fundi but no hemorrhages or exudates. Cardiac hypertrophy was present. The blood pressure varied from 168/90 to 180/105. The urine had a specific gravity of 1.010 but otherwise was negative. The blood urea was 46.74 mg. per cent. The serum protein was 6.59 mg. per cent. Urea concentration tests revealed slight but definite renal impairment. The combined phthalein test was 28 per cent for the first hour and 15 per cent for the second hour. Fractional phthalein test at the time of cystoscopy showed an excretion of 3 per cent from the left kidney and 7 per cent from the right kidney in the first fifteen-minute collection and 2 per cent from the left kidney and 5 per cent from the right kidney in the second fifteen-minute collection.

On April 29, 1938, under avertin-ether anesthesia, a left nephrocutaneous fistula (Goldstein's operation) was established after aspirating and puncturing the cysts on the cortical surface. The patient made an uneventful recovery and was discharged from the hospital on June 12, 1938.

During her second stay in the hospital a daily blood pressure chart was kept. Following operation her blood pressure gradually declined to 130/70. Subsequent blood pressure determinations were taken in the outpatient department at intervals of three months. The last blood pressure was taken on Nov. 19, 1940, and was recorded as 144/82.

At the time of each operation, a piece of renal tissue was removed for histologic study. Extensive fibrosis with chronic inflammatory changes and hyalinization of the glomeruli tubules and smaller blood vessels were noted in several areas. In other areas, typical changes, i.e., dilatation of tubules and hypertrophy of glomeruli, were observed. The sclerotic changes in the walls of the smaller blood vessels were graded 1+.

CASE 18.—(G. U., No. 1868.) C. P. L., white, male, 45 years of age, married, merchant, was admitted to the Sinai Hospital on Feb. 3, 1936. His family history was negative. The patient had had an appendectomy in 1917. In November, 1932, he had had pneumonia complicated by a lung abscess, which drained spontaneously and healed in six months. In 1933 he developed an infection of the left kidney following the lung abscess. He passed blood and was cystoscoped elsewhere, but nothing further was done about this condition. In 1935 he had hematemesis, accompanied by epigastric pain and tarry stools. The patient was confined to a hospital for three weeks but has had no further recurrence of this trouble. In the past three years he has developed dyspnea on exertion, increasing fatigue, backache, occasional vertigo and tinnitus, blurred vision, vague muscle and bone pains, and anorexia.

Examination revealed an abdominal mass in both upper quadrants which were round, firm, and nodular. Voided specimen of urine had a specific gravity of 1.008 and a trace of albumin; microscopically, it showed an occasional white blood cell and several red blood cells. Cystoscopy and pyelography revealed congenital bilateral polycystic kidneys. The red blood count was 2,750,000, 38 per cent hemoglobin; white blood count was 7,000 with 70 per cent polynuclear neutrophiles. Combined intravenous phthalein showed 4 per cent for the first half-hour; 6 per cent the second half-hour; 4 per cent the third half-hour; and 2 per cent the fourth half-hour. Blood creatinine was 5.2 mg. per cent; blood urea, 71 mg. per cent.

On Feb. 9, 1936, the left kidney was exposed and numerous cortical cysts were punctured and a nephrocutaneous fistula (Goldstein's operation) was established. The postoperative course was complicated by bronchopneumonia shortly after the operation. The patient was discharged on March 25, 1936. During the latter part of his stay in the hospital, there was a decided improvement in his general condition. The blood urea fell to 60 mg. per cent and the blood pressure, which on admission was 200/118, fell to 140/96. However, prior to discharge, his blood pressure gradually increased to 180/100. Following his discharge, he returned to his home in a neighboring state, but his general condition became progressively worse and signs of severe renal insufficiency developed and he died on Apr. 16, 1936.

A piece of renal tissue was removed at the time of operation for histologic study and revealed extensive fibrotic changes in the interstitial tissue between the cyst walls. There were relatively few blood vessels seen in the microscopic sections but the degree of vascular changes in these vessels was rather marked (grade 3+).

DIAGNOSIS

Hitherto the urologist and often the internist have assumed a rather casual attitude toward hypertension, a symptom complex which is so vital in its relation to the kidneys and yet so devastating in its possible effects on the mechanism of the body as a whole. With the development of cystoscopic instruments, roentgenographic procedures, and laboratory tests of great precision and immeasurable diagnostic and prognostic value, the internist has gained a more thorough recognition of the immense importance of lesions of the urinary tract in hypertension and the urologist has acquired the necessary confidence to undertake the difficult task of treating such cases.

A complete and accurate diagnosis in every case of hypertension depends upon a careful analysis and correlation of all diagnostic means at our disposal. A comprehensive study of the genitourinary tract appears to be one of the most important diagnostic aids available. Its diagnostic value is greatly enhanced when one considers the frequent occurrence of urologic lesions in hypertensive patients as indicated in the clinical statistics of Maher and Wosika, Schroeder and Steele, Williams and Harrison, and others. In establishing the correct diagnosis of an urologic disease, the urologist must be on guard and not overlook an accompanying chronic nephritis or secondary arteriolar changes in the kidneys whose presence can be detected only by skillful utilization of various renal functional tests. The latter lesions, if neglected or overlooked, may exert considerable influence upon the clinical course of the urologic disease or the hypertension and occasionally leads to diastrous results during the course of an apparently innocuous therapeutic regime or following a well-performed operation. The urologist must also be cognizant of the tendency of the Bright's disease to mimic or be confused with other lesions of the urinary tract.

A careful and complete urologic study entails the utilization of the following diagnostic measures:

1. An accurate history
2. Thorough physical examination including
   A. Blood pressure determination
   B. Ophthalmoscopic examination
   C. Special cardiac studies (i.e., electrocardiogram, teleroentgenogram)
3. Complete urinalysis
4. Laboratory tests
   A. Complete blood chemistry (i.e., urea N., N.P.N., creatinine, serum sulfate)
   B. Fractional phenolsulfonephthalein test
   C. Special renal functional tests (i.e., urine concentration, urea clearance, inulin clearance, and diodrast clearance)
5. Roentgenographic studies
   A. Plain film of the genitourinary tract
   B. Intravenous urography
   C. Retrograde pyelography
   D. Perirenal insufflation
6. Cystoscopic study
   A. Careful inspection of the lower urinary tract
   B. Ureteral catherization with collection of urine from each kidney for microscopic, chemical, and bacteriologic study
   C. Differential functional tests (phthalein, indigo, carmine)
   D. Bilateral retrograde pyelograms

A brief discussion of the pertinent features of each diagnostic method is herewith presented.

History.—An accurate history obtained from the patient or his family is an invaluable aid in the diagnosis and treatment of cases of hypertension associated with unilateral or bilateral diseases of the kidneys. Careful questioning will often reveal an antecedent infection or disease of the genitourinary tract whose effects or sequelae may have a direct etiologic relation to the hypertension. Attention must be directed not only to symptoms referable to the urinary tract but also to symptoms of other systems (i.e., cardiovascular) or organs (i.e., eyes) which may have a bearing on the problem at hand.

Physical Examination.—Having obtained a complete history, the next step is a thorough physical examination which should not be limited to the abdomen, genitals, and rectum but should cover the entire body. The general appearance of the patient should be carefully noted, as the keen observer can often discern some telltale signs of a constitutional disease or a specific organic lesion. Signs of renal insufficiency can often be detected. The urologist should not hesitate to avail himself of the services of an internist when evidence of cardiac pathology is found. Electrocardiogram and teleroentgenogram serve as useful adjuncts to the usual auscultatory examination and may be of inestimable value in determining the extent of the cardiac damage and the operability of the patient from a cardiac point of view. The urologist should familiarize himself with the use of the ophthalmoscope, for the presence or absence of vascular, inflammatory, or hemorrhagic changes in the fundi may prove to be of great assistance in differentiating between chronic

nephritis, nephrosclerosis, and chronic pyelonephritis. Changes in the caliber of the retinal vessels resulting from arteriolar disease, secondary to chronic pyelonephritis or a generalized disease process, may serve as one of the determining factors in the selection of cases of hypertension with unilateral renal disease suitable for nephrectomy.

Blood Pressure.—The routine determination of blood pressure is an essential part of every urologic examination. Urologists and internists alike are guilty of placing too much reliance on a single blood pressure reading obtained at the time of the initial examination. In view of the variability of the blood pressure in the same patient at different times, it is imperative that a blood pressure reading be taken not only at the start of the initial examination when the patient is nervous and apprehensive but also at, or near, the end of the examination, preferably prior to instrumentation, when the patient is in a more comfortable mental and physical state.

Blood pressure reading should be repeated at each subsequent office visit. When urologic patients suffering from renal calculi or infections are hospitalized, it is advisable to take blood pressure readings at least twice a day (in the morning and afternoon) for several days in order to rule out an associated hypertension. King and Keith stressed the advisability of taking blood pressure readings four times daily in urologic patients during the period of observation in order to detect the fluctuating type or paroxysmal type of hypertension. By this method variations due to nervous responses can easily be ruled out in patients suspected of having hypertension associated with unilateral or bilateral renal diseases, and the paroxysmal type of hypertension may be easily recognized in patients with adrenal medullary tumors. Following urologic operations, blood pressure readings should be taken daily. After discharge from the hospital, blood pressure should be taken at weekly intervals for the first few months, and later at monthly intervals.

There is no unanimity of opinion concerning the range of normal blood pressure. Robinson and Brucer made a detailed statistical study of the blood pressure in large groups of persons and concluded that the normal range of systolic blood pressure is between 90 and 120 mm. Hg and of diastolic pressure, between 60 and 80 mm. These figures are decidedly lower than those of other investigators. It is generally recognized that in normal children the blood pressure is lower than in adults and increases with age until at puberty it approaches the level of the adult.

Hines and his co-workers in the Mayo Clinic have made excellent intensive studies of the so-called normal blood pressure, its variations and its responses to the various tests. Hines recently studied the incidence of subsequent hypertension as correlated with the first reading of blood pressure which represented in most incidences the responses to nervous stress. It was found that excessive variations and excessive responses to the usual stimulation tests were indications of evidence of a possible

prehypertensive state. Patients whose blood pressure was not elevated as the result of nervous stress to more than 140 mm. systolic (or 85 mm. diastolic) are unlikely to develop hypertension subsequently; whereas, if the blood pressure under similar circumstances was less than 120 mm. systolic and 70 mm. diastolic, the patient was almost certain not to develop subsequent hypertension in the future. Conversely even transient elevation of the systolic and diastolic blood pressures into the upper range of normal are prognostic of probable subsequent hypertension. It was emphasized that elevation of the systolic blood pressure alone is not an indication of subsequent hypertension, which was more likely to occur when the diastolic pressure was elevated above the critical level of 85 mm. Hines recently maintained that heredity often determined whether or not a patient will develop hypertension as a result of renal disease.

Hines and Brown have shown by means of the "cold pressor test" that hypertensive patients show a greater response than do normal patients. The test was performed on a group of hypertensive children who were normal at the time of examination and revealed a positive response in a larger number of cases than in a similar group of nonhypertensive children. The cold pressor test consists of estimation of blood pressure immediately and at five-minute intervals, following the immersion of the hands or feet in cold water (4° C.) for a period of one minute.

Hardgrove, Roth, and Brown demonstrated a similar type of response with the inhalation of CO_2 and noted further that the responses were greater in the earlier cases of hypertension than in the advanced group.

LABORATORY TESTS

Laboratory studies of urine and blood are valuable aids in the diagnosis of urologic diseases. Unfortunately, there is no single laboratory test which affords a true evaluation of the renal function in every case. An accurate and complete estimation of renal function can be based only on the correlation of the findings of several different tests.

URINE EXAMINATION.—Urine examination must ever remain one of the most important steps in an urologic study, for much information can be obtained by a careful routine examination of the urine, preferably a catheterized specimen. As a rule, the determination of the specific gravity of a single voided or catheterized specimen is not of any great diagnostic value, but occasionally a low specific gravity may suggest the presence of polycystic disease or chronic nephritis. Hydrogen-ion concentration studies may provide valuable information from a therapeutic standpoint in the case of renal calculi and infections. Careful examination for albumin should be performed in every case in view of its significance in the early phases of renal pathology. Microscopic study of the centrifugalized urinary sediment is unquestionably a most important step in the examination of the urine, as the presence of ab-

normal urinary constituents, i.e., pus cells, casts, erythrocytes, bacteria, etc., is confirmatory evidence of renal damage. Erythrocytes are not ordinarily detected in the urine until the number exceeds 5,000 cells per cubic centimeter of urine. The extreme sensitivity of the orthololidine test warrants its use in every case in which erythrocytes are found in the urine; a 1+ test is obtained when the concentration is between 1,300 and 1,500 erythrocytes per cubic centimeter of urine; a 2+ between 4,000 and 7,000, and a 3+ between 5,000 and 20,000.

Blood Chemistry.—The chemical constituents of the blood are maintained in equilibrium by delicate adjustments of the filtration and secretion through the glomeruli and tubules. In kidney diseases this mechanism is easily disturbed with resultant changes in the blood chemistry. However, in the past too much reliance has been placed on the estimation of blood urea nitrogen, nonprotein nitrogen, and creatinine as tests of renal function. Recent studies have shown that a normal blood urea and nonprotein nitrogen may exist even when extensive renal damage has occurred, and that the values of these nitrogen serum elements show an appreciable increase only after 50 per cent or more of kidney tissue is destroyed. The blood urea nitrogen concentration may be considerably influenced by extrarenal conditions; i.e., dehydration, high protein diet, hypochloremia, alkalosis, hypotension, etc. Furthermore the increased blood urea and nonprotein nitrogen merely serve to indicate the inefficiency of the kidney to excrete protein waste products and are not a true indication of renal impairment. Mosenthal advocated the use of the urea ratio; i.e., the relationship between blood urea nitrogen and nonprotein nitrogen as a measure of renal insufficiency.

Recently Wakefield, Powers, and Keith demonstrated that serum sulfate estimation is a more valuable index of renal function than either the urea nitrogen, nonprotein nitrogen, or creatinine. They found that the upper limit of normal serum sulfate concentration is 0.5 mg. per cent. In cases of renal insufficiency, there is a parallel increase in the blood urea and serum sulfate. Lazarus has employed this test to great advantage in the appraisal of nephritic states in urologic patients and maintained that an increased urea nitrogen concentration in the presence of a normal serum sulfate is more indicative of dehydration than renal pathology. The urea nitrogen concentration may be disregarded when the serum sulfate concentration is within normal limits.

Renal Functional Tests.—The importance of measuring the renal functional capacity in health and disease does not require emphasis. These tests indicate the functional capacity not only of the kidney but of the whole body. Renal functioning tests are interpreted the best when correlated or supplemented by other available clinical and pathologic findings. Renal functional tests merely indicate the presence of an impairment in renal function but do not permit differentiation of primary renal disease from renal lesions secondary to intrinsic or extrinsic changes in the genitourinary tract and constitutional changes;

i.e., cardiac diseases, nervous diseases, abnormal metabolism, etc. Nevertheless, the functioning capacity of the kidney is a far more accurate index of the severity, course, and prognosis of renal disease than the degree of hypertension, hematuria, albuminuria, uremia, edema, etc. Unfortunately most of these tests necessitate quantitative chemical determinations which require special laboratories. Two tests of renal function are available to the urologist, internist, and general practitioner which can be performed with very little equipment and in a short time. Every urologist and clinician is fully acquainted with the use of the phenolsulfonephthalein test as a quantitative and qualitative measure of renal function, but few are cognizant of the fact that phenolsulfonephthalein is almost entirely excreted by the tubules with only 6 per cent excreted by the glomeruli, and that 50 to 70 per cent of the tubular epithelium must be damaged before an appreciable reduction in the total excretion occurs. The value of the test is limited by the presence of a complete or partial obstruction of the ureter, whereby tubular secretion is temporarily suppressed by back pressure or by the difficulty of collecting the urine trapped above the obstruction. The advantage of the test lies in the ability to determine accurately the rate of excretion over a two-hour period by noting the appearance time and estimating the amount of dye in the specimens collected every fifteen minutes, starting from the time of injection of the dye.

Shaw showed that the normal curve of elimination of phenolsulfonephthalein is characterized by an average output of 40 per cent during the first fifteen-minute period, 17 per cent during the second, 8 per cent during the third, 4 per cent during the fourth, and a gradual decrease to 0.5 per cent during the eighth period. Since the maximum excretion occurs in the first half-hour, collections of urine made at half-hour intervals will suffice for all practical purposes. The usual hour collections in vogue are impractical. All collections are dated from the time of administration of the drug rather than from the time of appearance of the drug in the urine. A record of the findings plotted in the form of a graph should be kept for future references and comparison. In the presence of vesical neck obstruction, it is essential that the bladder be emptied completely by catheterization or that an indwelling catheter be employed during the entire two-hour period. One cubic centimeter of the drug should be injected intravenously.

In a differential phthalein, which is performed with the catheter in each ureter, it is important to determine the time of the appearance of the drug in the urine, which is normally three to seven minutes. A large caliber Garceau ureteral catheter should be used to prevent leakage of the dye around the catheter. In differential phthalein, collections are made simultaneously from both kidneys during the same interval of time; i.e., preferably fifteen-minute and one-hour intervals; the starting point for the collections is the time that the dye is excreted from either side.

Indigo carmine is not quite as accurate as phenolsulfonephthalein, inasmuch as not more than 25 per cent of this dye is excreted by the kidneys. However, this dye is excreted more rapidly than phenolsulfonephthalein or methylene blue and its chief advantage is that it provides a rapid means of estimating the differential function of each kidney, of localizing the ureter, and of determining the presence of functioning renal tissue, especially in congenital anomalies and pathologic conditions of the kidney.

URINE CONCENTRATION.—The urine concentration test as described by Lashmet and Newburgh and modified by Fishberg is a very simple and yet one of the most delicate tests for renal function. This test demonstrates renal impairment in its early compensating stages. A brief outline of the test is as follows:

1. At 6:00 P.M. on evening before test high protein meal with not more than 200 c.c. of water is taken.
2. No fluid or food is taken thereafter until test period is over.
3. All urine voided between 6:00 P.M. that evening and 8:00 A.M. next morning is discarded.
4. Specimen of urine is collected at 8:00 A.M., 9:00 A.M., and 10:00 A.M. in separate bottles and specific gravity of each is determined.

Normally the specific gravity of at least one specimen will exceed 1.025. Renal damage is shown when the specific gravity is below that level. A specific gravity below 1.020 shows considerable damage. The test is not reliable in patients with loosely held edema, associated with congestive heart failure and occasionally in nephrotic syndrome.

Blood Urea Clearance Test.—The accuracy of the blood urea clearance test, as described by van Slyke and Cope, depends to a great extent on measuring the urea secreted in the urine during an exact interval of time. It is extremely important to obtain all urine formed by the kidney during the tests; consequently, catheterization of the bladder should be performed in cases of obstructive lesions of the vesical neck or urinary incontinence. The blood urea clearance test is less sensitive than the urea concentration test, for in many instances the urea excreting function of the kidneys becomes impaired after the concentrating ability of the kidney is diminished. The test determines the amount of blood that is cleared of urea per minute and its efficiency is dependent upon the passage of at least 2 c.c. of urine per minute, the so-called augmentation limit. The normal value (100 per cent urea clearance) is 54 to 75 c.c. of blood cleared per minute with an urinary excretion rate of 2 c.c. per minute. It is generally recognized that evidence of renal impairment is manifested only when the urea clearance falls below 70 per cent; a reading of 30 per cent or lower is of grave prognostic significance.

It is well established that the urea clearance and concentrating ability of the kidney in general parallel each other. In the cases of extensive

renal damage, the specific gravity of the urine may become fixed at a low level, and the urea clearance test then becomes the only indicator of the progressive changes in the kidney lesion. A low urea clearance is significant of renal damage, except when urine volume is less than 20 c.c. per hour. One disadvantage of the urea clearance test is that it requires two hours to carry through.

Smith and his associates have made important physiologic contributions to the knowledge of glomerular filtration rate, total mass of functioning renal tissue (tubular excretory mass), and rate of blood flow to this. They utilized clearance methods based on the capacity of renal tubules to remove certain foreign substances from the blood and excrete them into the urine, independent of glomerular activity. The desired blood levels of from 100 to 150 mg. per 100 c.c. of inulin and from 0.5 to 5 mg. per 100 c.c. of diodrast were maintained by means of slow intravenous priming and sustaining solutions of inulin and diodrast in 1 per cent saline solution introduced simultaneously. From 1,000 to 1,500 c.c. of water are taken orally before each test and not more than 200 c.c. of water given during the procedure. They showed that phenol red, diodrast, and hippuran are excreted by a common cellular mechanism in the tubules and that the tubular excretory activity is limited in that there is a maximal rate of excretion for each substance. They pointed out that no significant quantity of each of the three substances is stored in the renal tubule.

They found that the clearance of inulin and phenol red in normal men is quite constant. The minimal renal plasma flow, as measured by diodrast clearance, has an average value of 820 c.c. per 1.73 sq. m. surface area per minute which corresponds to a minimal whole blood flow of 1,384 c.c.

Diodrast clearance approaches closely enough a complete clearance to be considered identical with renal plasma flow. A study of thirty-four observations in 15 normal subjects indicated the effective renal blood flow ranging from 1,050 to 1,580 c.c. (average 1,339 c.c.) or 595 to 916 c.c. (average 772 c.c.) of plasma per 1,173 sq. m. per minute. The glomerular filtration fraction ranged from 15.3 to 21.8 per cent (average, 17.7 per cent). The glomerular filtrate rate is measured by inulin clearance (the normal inulin clearance varied from 113 to 137 c.c. per minute with an average of 122) and the filtration fraction (i.e., the apparent fraction of plasma cleared through the glomeruli) is obtained directly by inulin diodrast clearance ratio.

ROENTGENOGRAPHY.—There are several roentgenographic procedures available for the study of urologic patients suffering from, or suspected of having, hypertension: viz., (a) plain roentgenogram of the kidney, ureteral and bladder areas; (b) intravenous urography; (c) retrograde pyelography; and (d) perirenal insufflation of air. Each procedure has its indications and limitations which must be thoroughly understood if the procedure is best to serve the patient as well as the physician.

The value of each urographic procedure is dependent to a great extent upon the accurate and skillful interpretation of the various urograms which comes only through long experience with the normal findings and a familiarity with the various deformities and changes characteristic of early or late pathologic conditions in the urinary tract. Every patient subjected to any of the above procedures must be properly prepared in order to obtain good clear pictures devoid of shadows of collections of gas which may obscure or distort the urinary tract.

1. *Plain Roentgenogram.*—A plain roentgenogram of the abdomen taking in both kidneys and ureters as well as the bladder and prostate is indicated as a routine diagnostic measure (a) in every patient suspected of having a urologic lesion, (b) in every case of essential hypertension, and (c) in patients with vague abdominal symptoms or indistinct masses. In this many asymptomatic or unsuspected cases of urinary lithiasis, tuberculosis (with calcification), and renal neoplasms (with calcification) will be recognized which previously were erroneously diagnosed as some lesion of the gastrointestinal tract; i.e., appendicitis, cholecystitis, cholelithiasis, diverticulitis, etc. A plain film may also reveal changes in the adjacent osseous strictures which may have a significant diagnostic bearing on the case; i.e., changes in outline and density of vertebrae associated with arthritic or metabolic diseases, the presence of metastases in the vertebrae, ribs, and pelvis from a neoplasm within the genitourinary tract, or congenital or acquired developmental defects in the vertebrae associated with neurogenic disturbances in the urinary tract.

Great care must be exercised in differentiating calcified shadows overlying the kidney, ureter, bladder, and prostate in the absence of a complete urologic study, for not infrequently gallstones, calcified mesenteric lymph nodes, phleboliths, and papillomas are confused with or considered as evidence of renal, ureteral, or vesical calculi. The diagnosis is further complicated by the fact that the subjective findings associated with these extraurinary lesions may often simulate urologic lesions. It may be extremely difficult to interpret correctly the outlines of intraperitoneal and retroperitoneal tumors as distinguished from the normal or enlarged kidney or vice versa. In all such doubtful cases, an accurate diagnosis can be established only by resorting to other urologic diagnostic methods.

2. *Intravenous Urography.*—Excretory urography is of great value as a routine procedure in every case of essential hypertension and in puzzling urologic cases presenting atypical or vague symptoms. It is particularly valuable in those cases in which cystoscopy is contraindicated or impossible for various reasons. It has proved to be the best and frequently the only method for the demonstration of congenital anomalies of kidneys and ureters. This method also provides an excellent means of studying the function and dynamics of the kidneys. The diodrast clearance test as described by Smith and his associates is

the result of the observations on the excretory urographic changes and has served as an efficient measure of the total renal plasma flow. However, the correct evaluation of this test of the renal functional capacity must be correlated with other tests only when all factors responsible for the excretion of urine are known.

Intravenous urography has several shortcomings and limitations which should be realized by the urologist, radiologist, and clinician in order to prevent the indiscriminate use of such an extensive and time-consuming diagnostic method. Experience has shown that excretion urography is of little or no value in the diagnosis of renal tuberculosis, neoplasms and polycystic disease. Incomplete and irregular filling defects in the outline of the kidney, pelvis, and ureter which may simulate tuberculosis or neoplastic lesions of the kidney are frequently seen in patients with normal kidneys and an incorrect evaluation of these changes may lead to serious consequences from a diagnostic and therapeutic standpoint. The method is practically useless from a diagnostic standpoint in patients with minor degrees of renal infection (pyelonephritis) or extensive nonfunctioning pyonephrosis by virtue of its failure to demonstrate any anatomical changes. Intravenous urography should never be substituted for cystoscopy in cases of pyuria or hematuria. It is well to bear in mind that the mobility or failure to visualize one or both kidneys by this method is not necessarily due to a permanent, partial, or total impairment of the affected kidney. The same factors, which may interfere with the proper execution of phenolsulfonephthalein and other excretion tests of renal function, may operate in excretion urography.

3. *Retrograde Pyelography.*—This method obviously entails cystoscopy and ureteral catheterization. The method is practically indispensable for the accurate localization and identification of upper urinary tract disease. In my opinion, the only contraindications to retrograde pyelography are: (a) patients who do not tolerate instrumentation (i.e., aged, infirm, severe cardiac patients, etc.) and (b) hopeless patients in whom surgical interference is not possible and further information is unnecessary. With the perfection of cystoscopic instruments, refinement in cystoscopic technique, and development of innocuous pyelographic media, urologists no longer hesitate to perform bilateral pyelography. As a result of these advancements, we are now able to establish the correct diagnosis in the vast majority of cases. Retrograde pyelography is the most accurate procedure at our disposal in the diagnosis of renal neoplasms, polycystic disease, renal tuberculosis, and renal and ureteral calculi. It is the only reliable method for the graphic demonstration of the extent of the changes produced in the kidney by infection and calculi. Incomplete filling defects are not as likely to occur with this method, and in doubtful cases complete distention of the pelvis can be assured by employing pyeloscopy prior to pyelography. One cannot emphasize too strongly the value of ureteropyelograms taken in the

recumbent and upright positions and of an eight-minute retention film in the diagnosis of nephroptosis. Stereoscopic pyelograms are particularly helpful in the localization of renal calculi and in the diagnosis of renal neoplasms.

4. *Perirenal Insufflation.*—This method was introduced by Carelli in 1921 as a means of obtaining better contrast between the kidney and the surrounding tissue. In 1921 Quinby and in 1935 Cahill adopted the procedure for outlining the adrenals in cases in which these glands were suspected of hypertrophy or neoplasm. It has also been employed by numerous investigators in cases in which the adrenal gland was suspected of being the cause of paroxysmal hypertension. While this procedure is generally more useful in the diagnosis of adrenal enlargements than other methods, i.e., intraperitoneal air injections and intra-arterial injection of colloidal thorium oxide, it should not be adopted as a routine measure, as several cases of death from embolism have occurred following perirenal insufflation. The technique is simple and easily carried out in the x-ray room with a minimum amount of discomfort to the patient.

Criteria for Surgical Intervention.—It is extremely difficult to determine exactly which type of case of hypertension and unilateral renal disease is suitable for operative treatment. The experience and results of other surgeons emphasize the fact that an intensive study of each case is essential in order to select cases amenable to this form of therapy.

As a result of their extensive clinical study and a limited but well-rounded surgical experience, Schroeder and Fish have proposed five criteria to aid in the selection of cases for surgical treatment. I am of the opinion that these criteria admirably fulfill the necessary clinical and surgical requirements and urge their adoption by every genito-urinary surgeon called upon to treat such cases:

1. The arterial hypertension must be of recent origin (arbitrarily placed at two years).

2. The renal lesion must be confined to one kidney and must have produced a diminution in the function of this kidney.

3. The combined renal function of both kidneys, as determined by urine concentration and urea clearance tests, must be within normal limits.

4. Retinitis should be absent and the changes in the retinal vessels should be minimal.

5. The arterial blood pressure must be persistently elevated.

It must be remembered that the above criteria are applicable only to the employment of nephrectomy in the treatment of cases of hypertension due to unilateral renal disease and must not be interpreted as excluding from appropriate surgical treatment the large group of urologic cases with hypertension resulting from bilateral renal disease secondary to obstruction in the upper or lower urinary tract. For example, these criteria are not intended to cover cases of prostatic enlargement or

obstruction of both ureters by intrinsic lesions (i.e., stones, tumors, or strictures) or extrinsic lesions (i.e., infiltrations from uterine carcinoma) which are known to respond well to the institution of good urinary drainage by catheterization or appropriate surgical measures. Furthermore, urologists and clinicians must not overlook the fact that many cases of hypertension associated with unilateral or bilateral renal diseases exist in which reduction of arterial blood pressure cannot be accomplished by operation but in which relief from other distressing symptoms and general improvement may occur after operation. The symptomatic relief obtained after nephrectomy or nephrostomy in cases of large infected hydronephrosis or calculous pyonephrosis, even in the presence of a lesion in the opposite kidney, is too well known and too dramatic to justify withholding appropriate surgical treatment which may not have the least influence on the accompanying hypertension. Conservation of kidney substance remains today, as in the past, a consideration of fundamental importance whenever it can be effected with a reasonable degree of respect for the future comfort and safety of the patient.

Cases of hypertension associated with unilateral renal disease are occasionally encountered which fulfill the above criteria for surgical intervention but which either fail to respond to nephrectomy or are followed by a temporary or slight reduction in blood pressure with subsequent return to the preoperative level. Although an explanation of such untoward results is not always available or forthcoming, several possibilities suggest themselves: (1) the existence of a primary factor of extrarenal origin which has been overlooked; (2) the existence of arteriolar changes in the opposite kidney or elsewhere in the body which cannot be detected by our present diagnostic methods; and (3) hereditary hypertensive factor which has been suggested by Hines to explain why some patients develop hypertension as a result of a specific unilateral renal disease, and others do not, but also why some hypertensive patients fail to respond to nephrectomy.

Unfortunately, a certain amount of unwarranted enthusiasm has been engendered by the early reports of cases of hypertension associated with unilateral renal disease which were successfully treated by nephrectomy. One gains an entirely different outlook after analyzing the recent comprehensive reports of Schroeder and Fish and of Braasch, Walters, and Hammer which include a careful follow-up study of the blood pressure over long periods of time after operation. Their results have shown that nephrectomy is by no means a panacea and that its indiscriminate use is certain to be followed by the needless sacrifice of much valuable, though damaged, renal tissue and often with a disastrous result to the patient. In the treatment of hypertension associated with unilateral disease, it behooves the clinician and surgeon (1) to evaluate and correlate the clinical and urologic findings in order to select cases suitable to surgical treatment and (2) to weigh assiduously the relative

merits and efficacy of the various surgical procedures. It must be constantly borne in mind that nephrectomy is indicated only in carefully selected cases, as mentioned above, and is contraindicated in others. For example, nephrectomy offers no hope of reducing the blood pressure in cases of hypertension of extrarenal origin in which the presence of a unilateral renal disease bears no etiologic significance but merely represents a coincidental or accidental finding. Braasch, Walters, and Hammer have aptly summarized the contraindications to nephrectomy in cases of hypertension associated with unilateral renal disease. They maintained that nephrectomy should not be employed in the presence of (1) extensive bilateral renal disease, (2) extensive secondary degenerative changes in other organs, (3) advanced renal insufficiency, and (4) a serious unrelated but inoperable lesion elsewhere in the body.

SUMMARY OF PRESENT SERIES OF CASES

I have undertaken a review of 167 consecutive nephrectomies performed on the urologic service of the Sinai Hospital in the ten-year period Jan. 1, 1930, to Dec. 31, 1939, in order to determine (a) the relative incidence of hypertension in advanced unilateral renal disease, (b) the age and sex distribution, (c) the immediate and late effect of nephrectomy upon the hypertension in such cases, and (d) the correlation of the clinical findings and postoperative course of hypertension with renal parenchymal and vascular changes. I am cognizant of the limitations and dangers of drawing any definite conclusions from a small series of cases but present the following data in the hope that it will contribute in a small measure to the sum total of our knowledge of this subject.

A. *Relative Incidence of Hypertension in Unilateral Renal Diseases.*—In our clinic it has been the custom to consider a state of hypertension to exist in a given individual if the systolic blood pressure exceeded 145 mm. Hg and the diastolic pressure showed a corresponding increase usually above 90 mm. Hg. In this study I accepted the "mean" of all known preoperative blood pressure readings as the correct blood pressure of the patient whenever such data were available. However, in some instances we were forced to rely on a single blood pressure determination which was usually taken on the day before operation, i.e., several hours after admission to the hospital, and consequently the latter readings may be a few millimeters higher than normal due to the emotional stress and strain induced by the knowledge of an impending operation.

Hypertension was present prior to operation in 29 (17.3 per cent) of the 167 nephrectomized patients (Table I). This figure is slightly lower than that reported by Braasch, Walters, and Hammer, who observed hypertension in 315 (18.4 per cent) of 1,684 patients subjected to renal surgical procedures and in 195 (20 per cent) of a random group of 975 consecutive adult patients.

TABLE I

RELATIVE INCIDENCE OF HYPERTENSION IN 167 CASES OF UNILATERAL RENAL DISEASE TREATED BY NEPHRECTOMY

UNILATERAL RENAL DISEASE	ALL CASES	HYPERTENSIVE CASES (SYSTOLIC B.P., 145 MM. OR MORE)	
		NO.	%
Neoplasm	24	3	12.5
Tuberculosis	15	3	20
Pyelonephritis			
A. Acute	9	1	11.1
B. Chronic	9	1	11.1
Stone			
A. With Infection	44	13	30.2
B. Without Infection	9	1	11.1
Hydronephrosis			
A. Uncomplicated	4	0	
B. Complicated	16	3	18.7
Pyonephrosis	21	3	14.2
Traumatic	3	0	
Miscellaneous	13		7.6
A. Polycystic 2		1	
B. Ectopic Kidney 3		0	
C. Solitary Cyst 2		0	
D. Perirenal Cyst 2		0	
E. Hypoplastic Kidney 3		0	
F. Horseshoe Kidney 1		0	
Total	167	29	17.3

In Table I, I have classified the various pathologic lesions encountered and have indicated the relative incidence of hypertension in each group. As was to be expected, the incidence of hypertension varied widely in the different renal diseases. The percentage was highest in cases of renal calculi accompanied by chronic pyelonephritis. In this group of 44 cases of renal calculi with chronic renal infection the pathologic diagnosis was chronic pyelonephritis in 33 cases and pyonephrosis in 11 cases. Hypertension was present in 10 cases of stone and chronic pyelonephritis and in 3 cases of calculous pyonephrosis. We were greatly impressed by the fact that hypertension occurred most frequently in patients with chronic renal infection; viz., chronic pyelonephritis with or without stone, pyonephrosis with tuberculosis. Our clinical and pathologic findings substantiate the observations of Braasch, Walters, and Hammer: i.e., (a) chronic renal infection, accompanied by extensive atrophic changes in the renal parenchyma and sclerotic changes in the smaller renal vessels, is an important factor in the development of hypertension; and (b) the other clinical features of chronic renal infection, i.e., severity, duration, impaired renal function, pyuria, and pyelographic changes, do not appear to exert any appreciable influence upon the development of hypertension. The one case of hypertension associated with renal calculus without accompanying renal infection occurred in a male, 64 years of age, who had hypertensive cardiovascular disease. In our experience acute renal infections are rarely accompanied by hypertension as evidenced by the fact that pre-

operative hypertension was present in only 1 of 9 cases of acute surgical infections of the kidney; i.e., acute pyelonephritis with or without perinephritic abscess and renal carbuncle. Furthermore, there is some doubt as to the exact etiologic factor responsible for the hypertension in this 1 case as the patient was a female 60 years of age, who had been treated for hypertension for several years but was admitted and operated upon for an acute pyelonephritis and perinephritic abscess.

It is difficult to attach any significance to the high incidence of hypertension in renal tuberculosis in our small series. However, it is interesting to note that 2 of the 3 patients with hypertension had been previously treated for pulmonary tuberculosis in sanatoriums and had clinical evidence of active tuberculous lesions in other organs at the time of nephrectomy.

The incidence of hypertension in cases of hydronephrosis complicated by renal infection, ureteral stricture, and peripelvic adhesions was rather striking. Two of the 3 cases were encountered in our youngest patients, aged 19 months and 8½ years, who had congenital valves of the posterior urethra with bilateral hydronephrosis and congenital ureterovesical stricture, respectively. The third patient was a male, 52 years of age, who had a large infected hydronephrosis due to a stricture at the ureteropelvic junction.

There were only 3 cases of hypertension associated with renal adenocarcinoma in our series of 24 cases. These occurred in men past 50 years of age; viz., 52, 62, and 63 years. One patient had a calculus in the renal pelvis in addition to the renal neoplasm. In our series of 24 cases, the neoplasm was of the hypernephroid type of adenocarcinoma, with the exception of 1 case of papillary carcinoma of the renal pelvis.

B. *Age and Sex Distribution.*—It is difficult to evaluate the influence of age as a factor in the development of hypertension in so small a series of cases, particularly since 105 patients were below the age of 50 years. In our study the factor of age was particularly significant in explaining the comparatively high incidence (12.5 per cent) of hypertension in the group of 24 neoplasms since 18 of these patients were over 50 years of age and the 3 hypertensive patients were in this age group. The age may be considered an important factor in explaining the high incidence of hypertension in association with chronic renal infection since 11 of 15 patients with renal tuberculosis were below the age of 40 years and 25 of 44 patients with stones accompanied by chronic pyelonephritis were below the age of 50 years. The youngest hypertensive patients were two boys, 19 months and 8½ years of age respectively, who had nephrectomies performed for infected hydronephroses. The oldest hypertensive patient was a male, 64 years of age, who had a kidney removed because of hematuria due to a renal calculus but also suffered from hypertensive cardiovascular disease.

TABLE II

AGE AND SEX DISTRIBUTION OF CASES

AGE	NEOPLASM		TUBERCULOSIS		PYELONEPHRITIS (ACUTE)		PYELONEPHRITIS (CHRONIC)		STONE (WITH INFECTION)		STONE (WITHOUT INFECTION)		HYDRONEPHROSIS (UNCOMPLICATED)		HYDRONEPHROSIS (COMPLICATED)		PYONEPHROSIS		TRAUMATIC		MISCELLANEOUS		TOTAL NO. CASES	AVERAGE AGE	SEX		AGE DISTRIBUTION OF HYPERTENSIVE CASES
	Y*	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N			FEMALE	MALE	
1 to 9															2	1				1		1	5	4		5	2
10 to 19				1																1			2	18		2	
20 to 29		2	2	3		2		1		1		3		1		3	1	4				3	26	24.8	12	14	3
30 to 39		1	1	4		3		2	2	10	1	1				5		6			1	2	39	35.2	20	19	4
40 to 49		3		3				3	9	5	1			1				5				3	33	43.7	21	12	9
50 to 59	1	10				3	1	1	2	7		2		1	1		2	2		1		3	37	53	11	26	7
60 to 69	2	5		1	1			1		8	1			1		4		1					25	63.3	9	16	4
Total	3	21	3	12	1	8	1	8	13	31	3	6		4	3	13	3	18		3	1	12	167		73	94	29

*Y, hypertensive cases; N, nonhypertensive cases.

TABLE

SUMMARY OF 16 CASES OF

CASE NO.	NAME	AGE	SEX	DURATION OF HYPERTENSION	PREOPERATIVE OPHTHALMOSCOPIC FINDINGS	PREOPERATIVE RANGE OF BLOOD PRESSURE	POSTOPERATIVE RANGE OF BLOOD PRESSURE	NO. OF MONTHS OR YEARS FOLLOWED	LAST RECORDED BLOOD PRESSURE
1.	J. P.	52	M	3 yr.		200/100 210/110	166/ 96 170/100	152/108	3 yr.
2.	I. W. M.	50	M	5 mo. (?)	Markedly advanced hypertensive changes	220/116 228/124	140/ 98	260/140	3 mo.
3.	A. B.	36	F	1 yr.		160/ 90 168/ 98	140/ 90	140/ 90	2 yr.
4.	D. L.	21	F	1 yr.		148/ 86	120/ 80	120/ 80	4 yr.
5.	D. P.	24	M	1 yr.	Early hypertensive changes	144/ 92 150/ 96	122/ 78	120/ 78	2 yr.
6.	S. D.	48	F	3 yr.		188/100 210/110	124/ 60 138/ 70	158/ 92	13 mo.
7.	J. C.	49	M	2 yr.		166/ 84 174/ 92	140/ 80	132/ 80	3 yr.
8.	J. R.	52	M	2 yr.	Moderately advanced hypertensive changes	192/110 196/114	162/100 158/100	134/ 80 140/108	13 mo.
9.	R. C.	38	F	2 yr.	Normal	160/100 164/110	120/ 80	146/100	22 mo.
10.	R. G.	51	F	6 yr.	Markedly advanced hypertensive changes	220/120	140/ 90	245/135	2 yr.
11.	J. B.	8½	M	2 yr. (?)		140/ 84 160/100	135/ 80	120/ 82	7½ yr.
12.	C. J.	56	M	3 yr.	Moderately advanced hypertensive changes	180/120 186/124	140/ 90 144/ 92	170/110	4⅓ yr.
13.	M. K.	51	M	2 yr.		184/110 188/114	152/ 92	142/ 90	2 yr.
14.	W. T.	52	M	2 yr.		180/110 184/112	154/ 82	154/ 82	3 yr.
15.	A. W.	62	M	2 yr. (?)		168/ 86	140/ 80	140/ 80	1 yr.
16.	J. S.	63	M	3 yr.	Well-advanced hypertensive changes	220/110	162/ 88	162/ 88	8 mo.

HYPERTENSION TREATED BY NEPHRECTOMY

PREOPERATIVE DIAGNOSIS	PATHOLOGIC DIAGNOSIS	DEGREE OF VASCULAR CHANGES	REMARKS
1. Hydronephrosis (L) 2. Stricture at ureteropelvic junction (L) 3. Rupture of kidney (L)	1. Hydronephrosis 2. Acute and chronic pyelonephritis	++	Slight permanent improvement in blood pressure; plastic operation on left renal pelvis 3 mo. previously
1. Chronic pyelonephritis (L) 2. Solitary cyst (L)	1. Chronic pyelonephritis 2. Cortical abscesses 3. Solitary cyst	++++	Temporary improvement for 6 weeks followed by gradual elevation above preoperative level; died of cardiorenal insufficiency 4½ mo. after operation
1. Pyonephrosis (R)	1. Tuberculous pyonephrosis 2. Chronic pyelonephritis	++	Slight improvement in blood pressure; marked improvement in general health
1. Tuberculous kidney (R) 2. Tuberculous ureter (R) 3. Tuberculous bladder	1. Tuberculous kidney	+	Marked permanent improvement in blood pressure to date
1. Tuberculous pyonephrosis (R) 2. Tuberculous epididymitis (B) 3. Tuberculous orchitis (L)	1. Tuberculous kidney 2. Tuberculous orchitis	++	Marked permanent improvement in blood pressure to date (left orchidectomy 2 mo. previously)
1. Renal calculi (R) 2. Chronic pyelonephritis (R) 3. Stricture at ureteropelvic junction (R)	1. Chronic pyelonephritis 2. Kidney infarcts 3. Renal calculi	+++	Slight improvement in blood pressure; marked improvement in general health
1. Calculous pyonephrosis (L)	1. Chronic pyelonephritis 2. Renal calculus	+	Slight improvement in blood pressure; marked improvement in general health
1. Chronic pyelonephritis (R) 2. Renal calculi (R)	1. Chronic pyelonephritis 2. Renal calculi 3. Kidney infarcts	+++	Slight improvement in blood pressure; secondary ureterectomy 3 mo. later; marked improvement in general health
1. Calculous pyonephrosis (R)	1. Pyonephrosis 2. Renal calculi	++	Slight improvement in blood pressure; marked improvement in general health
1. Renal calculi (R) 2. Pyonephrosis (R)	1. Chronic pyelonephritis 2. Pyonephrosis 3. Renal calculi	++++	Slight temporary improvement in blood pressure followed by gradual return of preoperative level
1. Multilocular hydronephrosis (R)	1. Multilocular hydronephrosis 2. Chronic pyelonephritis	+	Slight improvement in blood pressure; marked improvement in general health (exploratory laparotomy 40 days previously)
1. Pyonephrosis (L)	1. Pyonephrosis 2. Chronic pyelonephritis	++	Slight improvement in blood pressure; marked improvement in general health
1. Pyonephrosis (R)	1. Pyonephrosis	+++	Slight improvement in blood pressure; marked improvement in general health (right nephrolithotomy 3 mo. previously)
1. Hypernephroma (R)	1. Hypernephroma 2. Chronic pyelonephritis 3. Chronic nephritis	+++	Slight improvement in blood pressure (died 5 yr. after operation of cerebral hemorrhage)
1. Hypernephroma (L)	1. Hypernephroma 2. Renal calculus	+	Slight improvement in blood pressure; slight improvement in general health
1. Hypernephroma (L)	1. Hypernephroma	+	Slight improvement in blood pressure (died 1 yr. after operation of cardiac failure)

The sex distribution of the 167 cases is shown in Table II. The cases of hypertension associated with unilateral renal diseases were practically equally distributed between the two sexes; viz., 15 males and 14 females. Eleven of the 14 females with hypertension were between the ages of 20 and 50 years and belonged to the group of chronic renal infection; viz., 2 tuberculosis and 9 stone with chronic pyelonephritis. The relatively high incidence of hypertension in females with renal calculi associated with chronic pyelonephritis may be explained by the frequent occurrence of such lesions in women of the childbearing age. Each of our 9 patients gave an antecedent history of either pyelonephritis of pregnancy or renal calculi or infection developing soon after pregnancy was terminated.

C. *The Effect of Nephrectomy Upon Hypertension Associated With Unilateral Renal Disease.*—A follow-up study of the postoperative course of the blood pressure was made in 16 of the 29 cases with hypertension as shown in Table III. In analyzing our results we were greatly surprised to find so few cases obtained a complete relief or a prolonged reduction of the hypertension as compared to the early enthusiastic reports of remarkable cures of hypertension following nephrectomy. Our best results were obtained in a relatively small number of cases in whom (a) the hypertension and clinical signs and symptoms of renal diseases were of comparatively recent origin (i.e., two years or less), (b) little or no impairment of renal function had occurred, and (c) no hypertensive vascular changes were present in the opposite kidney or elsewhere in the body.

Our results may be summarized as follows: (1) In every instance the removal of the diseased kidney was followed by an immediate but temporary reduction of the blood pressure for periods varying from three weeks to four months. It is difficult to determine to what extent this temporary lowering of the blood pressure is due to physiologic rest and inactivity during the period of convalescence or to a change in the pathologic physiology of circulation resulting from the removal of one hypertensive factor; i.e., the diseased kidney. (2) A striking improvement in postoperative blood pressure, which was manifested by a marked permanent reduction lasting from two to seven years, was observed in only 3 cases (Cases 4, 5, and 11). (3) A slight improvement of a permanent nature was noted in 9 cases (Cases 1, 3, 6, 7, 8, 9, 13, 14, and 15). Despite the removal of one hypertensive factor, these patients must be considered as remaining actually or potentially hypertensive. (4) Little or no improvement was observed in four cases (Cases 2, 10, 12, and 16). These patients exhibited a temporary reduction in blood pressure after nephrectomy which was followed in several months or years by a gradual increase in blood pressure approaching or exceeding the preoperative level. In retrospect the clinical course of 2 patients (Cases 2 and 10) was strongly suggestive of "malignant" hypertension.

The failure to obtain a striking or prolonged reduction in blood pressure following this form of therapy in the latter two groups may be attributed to either one or both of the following reasons: (a) the removed kidney was not the sole etiologic factor responsible for the hypertension, or (b) hypertensive vascular changes were present in the opposite kidney or in other organs which were not discernible by our diagnostic measures but which had progressed to a permanently irreversible status and militated against a good result.

We feel that a guarded prognosis must be given in every case of hypertension in which the removal of a diseased kidney is contemplated in view of the fact that a complete relief of hypertension or a marked permanent reduction in postoperative blood pressure is obtained in comparatively few cases; whereas, a slight temporary or permanent reduction is to be expected in the majority of cases. However, we are convinced that complete relief of hypertension can be expected in carefully selected cases which fulfill the preoperative criteria proposed by Schroeder and Fish for the selection of cases suitable for nephrectomy.

D. *Correlation of Renal Parenchymal and Vascular Changes With the Preoperative Clinical Findings and Postoperative Blood Pressure.*—With the assistance of the hospital pathologist, Dr. T. Weinberg, a special study was made of gross and microscopic features of each operative specimen in the 16 follow-up cases. Particular emphasis was placed on the degree of acute or chronic inflammatory changes, parenchymal atrophy, and vascular changes in small renal arteries and arterioles in each specimen. As a result of this study, we had hoped to establish a relationship between the pathologic finding and the preoperative and postoperative hypertension but found we were confronted with a mass of data which appeared to be inconsistent and even contradictory in some instances. From this meager amount of information we have hesitated to draw any specific conclusions or to correlate the pathologic findings with the hypertension. Nevertheless, certain pertinent observations were made from this limited series which appear worthy of record.

Every kidney removed in the 16 follow-up cases showed, in addition to the primary pathologic lesion, varying degrees of acute and chronic inflammatory changes as well as vascular changes in the smaller renal arteries. We undertook to classify arbitrarily the degree of vascular change in each kidney from grade 1+ to grade 4+, bearing in mind that the degree of vascular damage, as indicated in a limited number of histologic sections from each kidney, does not always serve as a true index of the degree of renal ischemia present. In our experience the best results from the standpoint of reduction in blood pressure were obtained in cases (i.e., Cases 4, 5, and 11) which had the least amount of vascular damage and parenchymal atrophy. On the other hand, we have observed 3 cases (Cases 6, 9, and 15) in which the degree of vascular damage and parenchymal atrophy was considered as minimal or scant,

but following nephrectomy only a slight improvement in the blood pressure of a temporary or permanent nature resulted. We have also encountered several patients, particularly in the group of renal calculi accompanied by chronic pyelonephritis and a pyonephrosis, who did not have hypertension but in whom extensive parenchymal and vascular changes were found. The latter findings serve as confirmatory evidence of the fact that unilateral renal diseases accompanied by vascular changes are not the only etiologic factors responsible for the development of hypertension.

Extensive vascular and parenchymal changes (grade 4+) were noted in 2 patients (Cases 2 and 10), who had the most severe degree of preoperative hypertension and obtained poor results following nephrectomy. Undoubtedly the recurrence of the elevated blood pressure in these cases after the temporary reduction incidental to the removal of the affected kidney may be attributed to the presence in opposite kidney and other organs of hypertensive vascular changes of an irreversible nature.

CONCLUSIONS

It is quite obvious that any clinical deductions, which are based on the analysis of the small number of cases of hypertension and unilateral renal disease reported in the literature and a personal experience limited to 16 cases, must necessarily be tentative and guarded. When the knowledge gained from such clinical surveys is supplemented by the observations and results of animal experimentation and pathologic study of autopsy material, there appears to be sufficient evidence to warrant the following conclusions:

1. The diagnosis of "essential hypertension" should be made with great reservations. Every patient with hypertension of unknown etiology should be subjected to a comprehensive study of the entire body, including a complete urologic study. The value of the latter type of investigation is emphasized by the frequent occurrence of urologic lesions in hypertensive cases as indicated in recent clinical and statistical reports.

2. The presence of a urologic lesion in a hypertensive patient must be carefully evaluated from an etiologic standpoint for not infrequently such a lesion is coincidental and bears little causal relationship but may influence considerably the clinical course of the hypertension.

3. There is a definite causal relation between hypertension and certain specific types of advanced unilateral renal disease; i.e., chronic pyelonephritis, hydronephrosis, ptosis, tuberculosis, Wilms' tumor, etc.

4. The same type of lesion occurs in many patients without the slightest elevation in blood pressure.

5. In certain selected cases appropriate surgical procedures, designed to remove or correct the unilateral renal lesion, have resulted in a considerable improvement in blood pressure findings.

6. In some cases the blood pressure returned and remained at a normal level following nephrectomy which may be attributed to the fact that the unilateral renal disease was the primary factor responsible for the hypertension and that secondary arteriolar changes in the opposite kidney or in other parts of the body were absent or had not progressed to an irreversible degree.

7. In other cases, the end results from the standpoint of reduction in arterial blood pressure were not as striking following nephrectomy; i.e., the immediate effect was a transitory lowering of the blood pressure for a few weeks or months followed by a gradual return to the preoperative level.

8. In a small number of cases, notwithstanding the fact that a definite causal relation between the hypertension and the unilateral renal disease could be established, neither an immediate nor late reduction in arterial pressure occurred after nephrectomy. This may be explained on the basis that either the unilateral diseased kidney was not the sole etiologic factor or the disease process had been present over a long period of time and had caused secondary arterial changes in its mate or elsewhere in the body which were responsible for the persistent hypertension.

9. It is important that an adequate period of time, at least one year, should elapse following operation before one attempts to evaluate the permanency and extent of the reduction in arterial blood pressure.

10. In view of the uncertain end results and insufficient period of observation in the reported cases, there appears to be no justification for considering nephrectomy as a panacea for the cure of hypertension in every case of chronic unilateral disease of the kidney.

11. Every case of hypertension associated with unilateral renal disease should be subjected to a careful and complete urologic study in order to select those cases suitable to operation and to prevent the needless sacrifice of renal tissue in those patients who can ill afford to lose same.

12. Every clinician and urologist should recognize the limitations and contraindications to nephrectomy in the treatment of hypertension associated with unilateral renal disease. It must be remembered that nephrectomy may be fatal in cases of hypertension of long duration or those whose clinical course is suggestive of the so-called "malignant hypertension."

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Review of Recent Meetings

THE SOCIETY OF UNIVERSITY SURGEONS

ALEXANDER BRUNSCHWIG, M.D., CHICAGO, ILL.

THE third annual meeting of the Society of University Surgeons was held at the Barnes Hospital, Washington University School of Medicine, St. Louis, Mo., Feb. 14 and 15, 1941.

The meeting was opened by **Evarts A. Graham** who gave a clinic on the advances of thoracic surgery during the past two decades.

Most of the papers presented at this meeting are to be found in this issue of SURGERY. Brief abstracts of other papers presented at that meeting are summarized herewith.

Max Taffel and **Sam C. Harvey**, Yale University: **Effect of Sulfanilamide on Wound Healing.**—Sulfanilamide did not appear to retard or inhibit the healing of stomach wounds in rats. Curves of healing of these wounds as measured by their tensile strength were practically identical in the control and experimental groups. Histologic studies of the wounds at each time interval revealed no striking differences in the two groups. The drug was administered orally.

Max Taffel and **W. J. German**, Yale University: **The Effect of the Local Application of Various Sulfonamides Upon the Brain.**—These experiments are still in progress and this report is a preliminary one. Sulfanilamide, sulfapyridine, sulfathiazole, and sulfanilylguanidine were applied respectively to the brains of monkeys, and histologic examinations made of the sites of application after four, ten, and twenty days. In the first group of animals the drug was placed upon the intact pia-arachnoid. In the second group a portion of the cortex was scooped out and the drug placed upon the exposed raw cortical surface. The local tissue reaction was approximately the same for all the drugs. It consisted essentially of a mild foreign body reaction characterized by the presence of variable amounts of multinucleated giant cells which had enveloped crystals of the drug. The studies thus far show that the cerebral tissue does not appear to be appreciably altered by the presence of the drug. Special stains are being investigated to verify this finding.

Warfield M. Firor, Johns Hopkins University: **The Use of Bactericidal Agents in the Colon.**—Preliminary evidence was obtained to show that sulfanilylguanidine markedly inhibited bacterial growth in the colon. The implications for colon surgery were discussed.

Joseph W. Beard, Duke University: **Purification and Properties of the Equine Encephalomyelitis Virus.**—Crude extracts of chick embryos diseased with equine encephalomyelitis treated with formalin lose all infectivity and subsequently possess the capacity to immunize against the active virus. The nature of the immunizing material has been the subject of much study. Information in this respect has been afforded by formalization of the purified virus under controlled

conditions. The product of such procedure has been practically indistinguishable by means of the analytical ultracentrifuge from the untreated virus, indicating that the essential immunizing component is comprised in the main of an inactive formalin product of the virus. Under proper conditions, an identical material can be obtained from the crude vaccines.

Henry Poer, Emory University: **Lymphosarcoma of the Duodenum. Case Reports.**

Alexander Brunschwig and **Richard A. Rasmussen**, University of Chicago; **Benign Neoplasia of the Stomach and Diet.**—Rats on various types of deficient diet develop ulceropapillomas and papillomas of the rumen and true stomach. This is a manifestation of a certain degree of malnutrition, the latter being of no specific type.

I. Ridgeway Trimble, Johns Hopkins University: **The Role of Vasomotor Spasm in Peripheral Arteriosclerotic Disease Following Sympathectomy.**—In forty patients with arteriosclerotic peripheral vascular disease, lumbar sympathectomy has been performed, with results suggesting that the spastic element plays a role in the production of intermittent claudication, pain, and gangrene.

Book Review

Entre Cirujanos y Hospitales (Among Surgeons and Hospitals). By Dr. José Castro Villagrana, Mexico City, 1940, published in Spanish by the author. 1 vol., pp. 202.

At this moment when the terms Pan-Americanism, Pan-American Union, Pan-American Congress, etc., are heard everywhere as the expression of the growing importance of Latin-American cooperation in harmonizing the common interests of the democracies of the Western Hemisphere for their mutual good in every sphere of their international relations, messages of good will and professional fraternalism are particularly welcome. Such is the message conveyed by Dr. José Castro Villagrana in his remarkable memoir of travel in American and Europe, entitled *Among Surgeons and Hospitals* which is now before us.

It is surprising that despite the fact that Mexico has become in recent years the magnetic center of attraction to the American tourist, and despite the enormous literature that is piling up on every phase of Mexican history and Mexican life, there is so little known or written on the medical institutions and medical activities of our neighboring republic by the profession on this side of the Rio Grande. For this reason the opinions and observations of a capable and thoroughly representative observer of our own institutions, even though limited to the surgical sphere, are well worthy of extended notice.

This is a remarkably interesting narrative of travel by a Mexican surgeon gifted with an artistic temperament and a fine scholarly capacity for describing and reflecting on what he sees and hears. Despite the total exclusion of all official titles, the author of this memoir (who could display them in profusion) is too well known as one of the outstanding and most progressive surgeons of the younger generation in Mexico City to require them.

As professor of surgery in the faculty of the medical school, director and chief surgeon of the Juarez Hospital, one of the largest (2,000 beds) and one of the oldest in its historical foundations, Dr. Castro Villagrana has been largely instrumental in introducing many innovations in surgical education and in rebuilding and completely modernizing an obsolete old hospital, formerly the San Pablo, which traced its origin to a sixteenth century (1569) Franciscan church and school for Indians, serving later as barracks and military hospital until 1872, when it became the Juarez Hospital.

Besides the epochal architectural and administrative transformation that the Juarez Hospital has undergone during the period of Dr. Castro Villagrana's incumbency, he has been a pioneer and tireless leader in the most recent movements that tend to unify the surgeons of his country in a constant effort to increase the efficiency of their hospitals as community centers for surgical relief and the training of surgeons. All of this is attested by his initiation and participation in the founding of the important Surgical Society of Juarez, in the National Association and Assembly of Mexican Surgeons, the National Hospital Association, the Mexican Society of Anesthetists, the Training School for Nurses, the establishment and development of social service in hospitals and in the organizations of the student body that tend to fit them for the higher responsibilities of the medical profession.

Always keenly alert and responsive to the students' needs, it is not surprising that he should be one of their best loved teachers.

Chiefly concerned in the progress of surgery and anxious that its teaching and practice at home should not suffer by comparison with those of other countries, Dr. Castro Villagrana, following the example of his lamented preceptor, Dr. Ulises Valdez (an honorary fellow of the American College of Surgeons), sought opportunities early in his career for observation and technical improvement in the great surgical clinics of the United States. How he gathered a rich harvest by his visits to the surgical centers of St. Louis, Chicago, Rochester, Minn., Baltimore, New York City, and Boston, is graphically told in paragraphs glowing in admiration for the work of the Mayos, Crile, Cushing, Dandy, and many others of whom he speaks collectively as the "Titans" of American surgery. He returned to Mexico deeply impressed with the splendor and vast resources of American medical schools and hospitals, the solidarity and marvelous rise of surgery as a specialty, the vast multiplication of surgical societies, and the creation of examining boards to test the qualifications of its candidates for practice; the standardization of hospitals inaugurated by the American College of Surgeons, the American Medical Association, and with it the enormous progress in surgical and hospital care which these great institutions had accomplished.

The opportunities for the special training and education of surgeons impressed him as being greater and more liberal in the hospitals of the United States than anywhere else in the world. His admiration for the American nurse evokes an outburst of praise, virtually an apotheosis, which could be well quoted in its entirety as an eloquent salutatory for a graduating class in American training schools.

The author's observations in this and other journeys to the United States are characterized by a remarkable clearness of observation, total absence of prejudice, a discerning judgment, and a friendly appreciation of what is best in our institutions. That these observations have had their influence in his own country is quite evident in the over-expending program of hospital construction and rehabilitation and professional organization that is so notable in Juarez and other great hospitals of the Mexican metropolis.

Years later, in another journey to the United States, he stopped with several members of his staff to study the new Charity Hospital, in New Orleans, La., which was then under construction, and the medical institutions of the city, which, more than any other in North America, holds the greatest appeal to the Latin American traveller.

It was then that, through a happy circumstance, well described in this book, Dr. Castro Villagrana and his party arranged to meet Dr. Matas whose authority in vascular surgery had been long recognized in Mexico, where his operations for the cure of aneurysm were taught in the medical schools.

Indubitably one of the most fascinating chapters of the book is the author's brilliant portrayal of Dr. Matas. With glyptographic keenness the author first presents his impression of the general appearance and the noble beneficent countenance of Dr. Matas. As he unfolds his character study of this master surgeon, there is brought to light in gleaming and transpicuous rhetoric his multifaceted charming personality. In worshipful admiration he vividly portrays Dr. Matas' keen sense of humor, his effervescing vivacity, his beneficent cordiality, his contagious enthusiasm, his innate modesty, his linguistic perfection and facile eloquence, and his amazing knowledge of music, art, and history. In brief biographical sketch he traces concisely Dr. Matas' successful career from a young surgeon to that noble pedestal reserved for those whose life has been devoted to an eager and unceasing effort to benefit mankind. Referring succinctly to the numerous innovations and advances that have characterized his surgical enterprise, his perspicacious clinical and experimental investigations, and his invaluable contributions on surgery of the vascular system which

have made his name inseparably linked with this branch of surgical endeavor, in deservedly glowing terms, the author's tribute clearly reflects the world-wide appreciation of Dr. Matas.

The international amenities and friendships that resulted from this visit to New Orleans and Dr. Matas' cordial reception are stressed by the author in his reflections on the often unsuspected benefits that accrue to the nations from the interchange of medical relations, the medical man in his modest sphere officiating as a true ambassador of peace in a troubled world sown with the seeds of hatred, discord, and destruction.

In 1938, an opportunity to visit the great surgical clinics of Europe came with the triennial congress of the International Society of Surgery (Societé Internationale de Chirurgie) held in Brussels, September, 1938, to which he had been officially and automatically delegated as chairman of the Mexican branch of this world-wide and truly representative international organization. Furthermore, the fact that his friend, Dr. Matas, as president of the Society, would preside over the congress, gave an additional incentive to attend it.

The narrative of Dr. Castro Villagrana's odyssey through the surgical clinics of Europe begins in London and continues for five chapters devoted to the surgeries of the continent, with long stops in Paris, Rome, Bologna, Padua, Vienna, Munich, Berlin, Dresden, Hamburg, and ending in the Congress at Brussels, which alone furnished him a complete cross section as it were of the best in the world of surgery.

Throughout this varied and colorful travelogue, the narrative moves along with all the animation of a technicolored cinema in which the master surgeons of the world are depicted in their typical surroundings and most characteristic bodily and mental attributes. Dr. Castro-Villagrana reveals his artistic, literary, and journalistic ability by the ease with which he transmutes into words whatever he visualizes. His first thought immediately after his introduction to the surgeon and his clinic, whether in his operating theater or in his private study, is to secure a mental snapshot that is to serve later for his comments and reflections on the man and the scene, always informative, biographic, and often meditative and philosophic. In this way his travelogue becomes a portrait gallery of master surgeons and of their characteristic environment, all told with a simplicity, fairness, and kindness, which make his impressions and judgments worthy of trust and confidence.

The International Congress at Brussels, with its splendid aggregation of the elite of European and International Surgery, afforded an excellent opportunity to Dr. Castro Villagrana to exercise his literary talents as a word painter to great advantage. In fact, his miniature sketches of the thirty and more members of the International committee assembled from every quarter of the globe, seated around the council table, suggest a large mural of mosaic tablets in which the facies of each one of the delegates can be plainly recognized in the word pictures of his vigorous strokes.

In this book the scientific proceedings of the Congress, which covered great discussions on some of the most vital issues in contemporary surgery (arterial hypertension, pulmonary surgery, bone grafting, etc.) are interestingly described in a language which is technically correct and yet thoroughly intelligible to nonprofessional readers. The program for the Twelfth Congress, which was to have been held in Stockholm this September (1941) under the local management of Dr. Hybinette and his Swedish colleagues, had been planned for a scientific feast of unsurpassed interest for the surgeons of the world, but the unexpected death of the lamented Prof. Hybinette, no doubt precipitated by the menace of a Nazi invasion of Sweden, has shattered all prospect of a congress in Europe for probably some years to come. Fortunately, the great organization, founded in 1905, is built on a foundation as immutable as the Rock of Ages, and is too well rooted in all civilized

countries, including the United States and Canada, to suffer more than a temporary suspension of its international functions.

We may rest assured that the Societé Internationale de Chirurgie will pursue its magnificent traditions and manifest destiny when the tempest now sweeping over the suffering and delirious world has blown over.

Finally, to close this very inadequate notice of Dr. Castro Villagrana's fine book, we must touch, if only for a moment, upon his last chapter, "On the Surgeon and his Responsibilities," which sums up the most profitable lessons of his peripatetic experience.

In the vast surgical panorama unfolded by his travels, he has been struck by the constantly increasing importance of surgery in the social order, by the solidarity of its organizations and by the variety of its practitioners; none seemingly perfect but many great, and the greatest always those who never ceased to strive and labor honestly and sincerely for their own self-improvement in the service of their fellows and their art.

Whatever his exteriorizations, the surgeon must possess at least three fundamental qualities for success: *security or safety*, born of knowledge, skill, experience, and moral conscience; *gentleness*, kindness and tenderness with firmness, which comes from respect of human life and for the flesh itself, which the surgeon molds, trims, and fashions to accomplish his curative and reparative ends; and *simplicity*, which means directness, straight paths, not complicated or circuitous detours in thought or action, not burdened with time-wasting superfluities.

And those are the qualities which, according to those who know him best, are most distinctive of the author himself.

In conclusion, Dr. Castro Villagrana has produced a book that honors the surgical literature of his country, and that is elevating to the dignity and moral tone of surgery in general. In its ideology and literary quality it is essentially the product of a Latin mind; in its spiritual uplift, it is the expression of the noblest aspirations of mankind as voiced by one of the most fervent devotees of the cult of Esculapius.